On Goals and Habits: Lessons from deep brain recordings in Humans Zur

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On Goals and Habits: Lessons from deep brain recordings in Humans

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Contents

1 Introduction

The human brain is able to perform similar motor actions using different cognitive strategies. For example, picture yourself walking slowly on a small trail embedded in a flat meadow in the Swiss alps surrounded by blue mountain gentian. Depending on your interest, you might try to remember the latin name of the flowers surrounding you [1], or try to get to the bottom of a work related problem. However, the rhythmic movement of your legs barely come into awareness and perform their movement almost autonomously. In contrast, when you walk in a similar pace on a similar trail (in terms of narrowness and topography of the path), which is now placed on top of an exposed ridge of a rocky mountain, you probably consider every step carefully, planning the next movement of your foot in order to optimize the outcome of your motor actions (i.e. staying on the path), and maximizing your reward (i.e. returning home safely). The names of the mineral rocks on the ridge or your work issues probably do not cross your mind whatsoever. Motor performance in terms of step size and speed might be very similar in both scenarios, but apparently a different strategy is implemented in the brain to perform the desired action. In the first scenario walking is performed as a highly over-learned and automatic action - a habit. Habitual performance mainly is guided by sensory feedback (e.g. perception of touch with each step) allowing for a rapid and effective 'automatic' control of the ongoing motor output. Conversely, in the second example, motor performance is guided by a constantly updated and controlled association between motor action and planned outcome: each step is evaluated according to its actual outcome. The previously experienced habitual control of walking is replaced by a more cognitively guided and fatiguing, slower process: Walking on the trail is now a goal-directed movement.

This intuitive dichotomy has inspired many experimental paradigms of motor control comparing acting strategies in goal-directed and habitual motor behavior, respectively [1, 2]. Depending on the theoretical background, different frameworks are provided in the literature for these opposing poles of behavioral control. In terms of cognitive neuroscience the framework is that of reflexive and reflective [3] behavior for habitual and goal-directed strategies. Learning theorists use the concepts of instrumental control to describe goal-directed and habitual behavior in terms of stimulus-response (S-R) and action-outcome (A-O) driven decision making and learning [4, 5, 6]. On more theoretical grounds, using formal computational theory of reinforcement learning, 'model-free' versus 'model-based' control or implicit versus explicit strategies are introduced and implemented for the same dichotomy [7].

From a neuro-anatomical perspective, the identification of separated parallel neuroanatomical cortico-subcortical networks provides an excellent, yet hypothetical structural correlate for a functional segregation of motor control depending on the currently implemented cognitive strategy [8, 1]. Parallel cortico-subcortical loops have been identified in humans [9, 10, 11], as well as non-human primates [12, 13, 14]. And imaging studies support the idea of segregated networks by identifying different patterns of cortical activation

[1] it is the botanic family of genianaceae

depending on current environmental settings for a specific task [15, 16, 17].

Although these theoretical concepts share the dichotomous theoretical structure of behavior that is explicitly 'cognitively-driven' on the one side and automatic or implicit on the other, they are applied in different experimental frameworks and are therefore associated with certain 'technical' and experimental differences. For instance, in rodent experimental literature, the term 'goal-directed' is interpreted almost exclusively in terms of reward learning: Motor behavior is linked to a (physical) reward, typically in form of food. Animals are first trained to perform a specific task (action) to receive a reward (outcome). Habitual behavior is then defined as persistent motor behavior in absence of the previously present reward (the defining property of stimulus response). However, human behavior is often not directly associated with immediate physical reward, so how can these concept be translated to more complex human behavioral tasks? Furthermore, the post-hoc definition of a habit as persistent (involuntary) behavior in absence of a reward, requires a previously established explicit action-reward association. However, in many habitual and overtrained behaviors in humans (e.g. walking) there is no obvious (a priori) action-outcome contingency which is later devaluated.

Form a more computational perspective, model-free and model-based behavior are developed from concepts of reinforcement learning [18]. Model-based control refers there to the application of " sophisticated, computationally demanding, prospective planning" [19] . A mental decision tree of possible future states and actions is required to conceptualize motor behavior depending on the desired output. Thus, on the most abstract level, model-based control can be regarded as any process that requires an internal prospective cognitive model or a 'cognitive map' to decide for and implement a certain motor behavior [20, 19]. In contrast, model-free habitual behavior is retrospective and based on memory, rather than 'online' explicit decision making and is therefore faster and cognitively less demanding. Importantly, in this broader sense, these concepts can be applied to motor behavior without the need for reward and devaluation of rewards.

These concepts are summarized in the following sections, where I will outline the advantages and limitations of these complementary approaches. As a theoretical expansion, a novel integrative model which includes aspects of both theories in a multimodal framework will we introduced. This approach was pursued to understand and apply the concept of goals and habits in human motor behavioral studies in variable settings and experimental paradigms. Using this theoretical framework, I will contextualize and discuss three different behavioral motor studies, which will be analyzed in a comparative approach in the light of shifting brain network activity in goal-directed and habitual behavior. Specifically, I will discuss a standardized gripforce task [21], cued (goal-directed) finger tapping [22] and movement in REM sleep [23] using the overarching framework of goal-directed and habitual behavior. All paradigms were performed in awake patients with intracranial recordings from the subthalamic nucleus. Therefore, these experiments allow for a comparison of the electrophysiological brain network state in the studied behaviors between and within

these paradigms.

1.1 Goals and Habits in Terms of Learning Theory

Classical theories of instrumental behavior distinguish between two competing theoretical frameworks for learning. Stimulus-response (S-R) learning is based on the formation of associations between an environmental stimulus with a related action [24]. During learning, behavior is linked to outcome by reward or punishment (reinforcement), however with increasing experience this association is reinforced and eventually 'stamped in' and response to a stimulus occurs independently form the realized inhibited or devalued outcome [5, 25] The classical example for S-R action is an animal that was conditioned to press a lever for food reward, but continues to press the lever even if the outcome is extinct or devalued (e.g. mixed with nauseating substance) [26, 27]. In terms of the broad terminology introduced in the introductory paragraph, outcome insensitive S-R behavior corresponds to habitual control [28]. On the other hand, in situations where a relationship between a changing stimulus and its corresponding outcome is maintained, instrumental behavior is considered to be under action-outcome (A-O) control. In contrast to S-R control, in A-O learning there is no dissociation of the response (action) and its corresponding outcome. In other words, the contingency (i.e. the subjective causality) between response and its outcome (in terms of instrumental learning usually reward or punishment) remains intact and therefore relevant for behavioral decisions [6, 29, 30]. Hence, an animal operating under A-O control would stop pressing a lever, if the corresponding outcome is devalued; A-O control corresponds to goal-directed behavior [29].

From an experimental point of view, this framework allows for establishing certain well-defined criteria to determine whether goal-directed (A-O) or habitual (S-R) learning dominates. The hallmark of habitual behavior is the loss of association between outcome and action (by 'shortcutting' via stimulus-response association), purely habitual behavior is indifferent to (i) devaluation of a rewarding outcome and (ii) degrading contingency between a certain outcome with a previous action [31]. The latter can elegantly be accomplished by introducing interval dependent and ratio-dependent modification to an action-outcome contingency. Fixed interval paradigms in which reward is delivered after a certain (fixed) time period, promote habitual behavior, because the the predictability for a favorable outcome (contingency) is low, whereas a fixed ratio paradigm (reward is delivered after a fixed amount of lever presses) favors goal-directed (A-O) control [32, 33, 26].

This dichotomy was and still is a fruitful (yet controversial) framework to study neural network correlates of habitual and goal-directed behavior predominantly in animal models and gave important neurophysiological and neuroanatomical insights [26]. Nevertheless, the 'binary' concept (S-R vs A-O) also has certain limitations. Importantly, these concepts are first of all not exclusive and tend to occur for similar task in

tandem [34]. Typically, novel tasks are under A-O control (goal-directed), whereas with sufficient repetition S-R tends to dominate. However, also rapid transitions between both frameworks are possible within short time, for example when previously established habitual behavior interferes with goal-directed control in a changed environment (slips of action) [35]. In other words, alternative circumstances allow alternative behavior, regardless of previous behavioral conditioning [36, 37, 38] . Second, these behavioral paradigms represent the black and white extremes of instrumental behavior of what is more likely to be a continuum. Furthermore, both types of behavior are implicitly linked to (1) environmental cues (e.g. a lever) and (2) a provided, absent or devalued reward (e.g. sucrose). However, in humans both cue and action-related rewards are not strictly necessary for motor learning and instrumental behavior per se. For instance, habitual movement (e.g. walking) can be performed in a self induced pace without present environmental salient cues and motor learning might occur in absence of imminent reward feedback. From a theoretical perspective, tasks requiring higher lever cognitive processing and decision making are difficult to conceptualize within an unidimensional action-outcome relation [39, 40, 41] and basic reinforcement learning methods are not effective in describing complex paradigms with a large set of possible actions (scaling problem, see [42])

1.2 From S-R/A-O towards Model-free and Model-based Cognitive Strategies

In a more computational approach, this dichotomy is extended into a novel framework implementing ideas from computation theory and dynamical programming [36, 43]. In this approach, habitual (S-R) behavior is conceptualized as 'model-free' motor control, indicating the absence of a higher 'cognitive' concept linking a stimulus to a certain behavior (e.g. absence of contingency). Model-based behavior on the other hand entails processes that are under permanent control of an internal model linking the current state to all possible outcomes within a tree-like decision algorithm [44, 45]. Derived from ideas in dynamical programming [46], the probabilistic structure between a current state (and stimulus), a behavioral response and outcome is permanently updated and evaluated for each decision, providing an accurate but computationally (cognitive) highly demanding process. This broader theoretical approach allows for a more general application of the dichotomy in terms of behavioral (motor) execution paradigms [47, 44, 48]. For example, unlike classical S-R and A-O paradigms, the use of an 'internal model' in charge of (goal-directed) control does not require a physical cue or reward to relate a stimulus to and action. In very general terms, instrumental behavior is modeled as state-to-state transitions with either guided by an internal cognitive model (model-based) or free from application of a cognitive strategy (model-free). Furthermore, these categories are not intrinsically linked to learning of novel task (and eventually habituation). In this broader sense, over-learned tasks can rely on model-based or model free conditions depending on the corresponding environment or paradigm shift, as outlined in the following section.

1.3 Goals and Habits in a Multimodal (Behavioral) Framework

As developed in the previous section, contextualization of goal-directed and habitual behavior in classical theory of reinforcement learning leads to the rather procedural definition of habitual behavior, as over-learned behavior that persists after dissociation of outcome and action (e.g. by de-valuation). This is a useful and valid approach, and in particular in animal models a rigid dichotomy can be established free from subjective cognitive measures (which are not approachable e.g. in rodents). However, this definition links the execution and building of habits intrinsically to reward learning [49]. Strictly speaking, model-based predominance can only be observed in an over-trained state and conversely goal-directed behavior occurs per definition only early in the learning phase (or after a change of environmental cues). The formulation of this theory in more general terms (model-based vs model-free) liberates this rigid definition from explicit dependence on behavioral measures and can be used to determine the actual predominant cognitive strategy. This is an advantage over the procedural definitions of goal-directed and habitual control in learning theory, because by defining habits post-hoc as persistent motor output after devaluation, each behavior must be either completely goal-directed or habitual in a kind of 'winner takes it all' framework. As an important extension, the framework of model-based and model-free strategies allow for occurrence of both systems in concert. Indeed, Daw and co-workers [36] found that in a simple behavioral task, model-based and model-free control is executed and linked to striatal neuronal activity (BOLD-MRI) at the same time. Therefore, a certain behavior might be predominantly model-driven, but with a certain model-free (habitual) contribution.

Importantly, in this view the temporal aspects of learning (i.e learning to rely more on the habitual model-free system during and after practice) shares the same structure with cognitive flexibility (i.e. change of cognitive strategy based on a change of the environmental setting). In general terms, these concepts are summarized in a generalized model based on temporal and environmental aspects of instrumental control as shown in Figure 1.

There are, however, limitations to the association of habits with model-free and goal-directed behavior with model-based learning. First, if both systems work in concert, a higher level mechanism must 'decide' which framework is to be executed to most efficiently provide a certain behavior [27]. The uncertainty of a model has been proposed as a decision algorithm control behavior via model-based or model-free systems [39]. However, from a behavioral perspective, this argument transforms the core question (when is habitual or goal-directed behavior in charge) only to a higher level. Also from a theoretical point of view, model-free reinforcement learning fails to reproduce the de-sensitivity of habits to contingency degradation. Furthermore, by applying this definition, the transition from goal-directed to habitual movement is imperatively linked to (dopaminergic) reward learning. As a consequence, this transition is a one-way road; once a habit is acquired, it persists as a over-learned cognitive strategy and dominates behavior in the same setting. How-

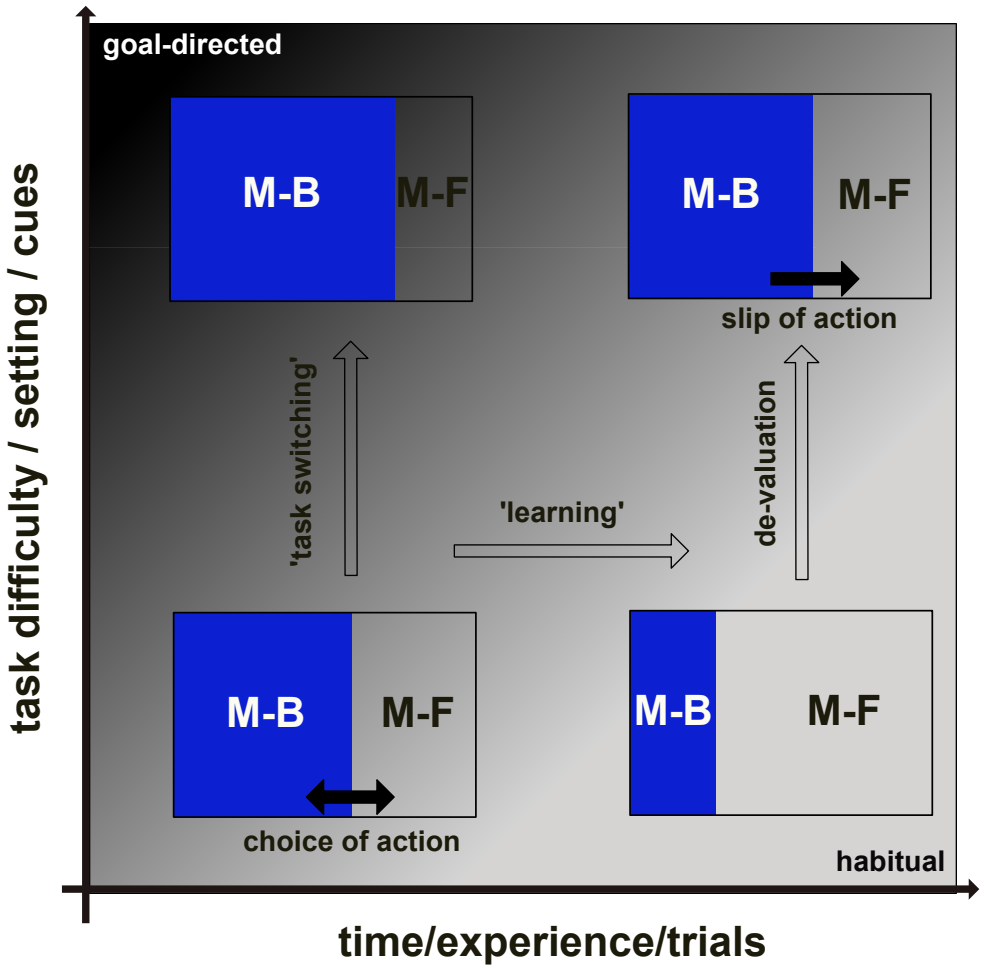

Figure 1: Goal-directed and habitual behavior in a multimodal framework. Task setting (y-axis) and experience (x-axis) influence the predominantly used strategy for motor execution. Model-free (M-F) and model-based (M-B) motor control work in tandem with variable predominance depending on task setting and experience.

ever, a change of environmental cues can provoke a sudden 'unlearning' of a previous well established habit. Consider the example in the introductory anecdote. Habitual walking is suddenly replaced by goal-directed walking by change of the environmental cues. One might argue that the frightening walk on the ridge is simply a novel introduced and unknown task, which will end up in habitual behavior eventually, but the motor behavior will probably not reach the same amount of automaticity as on the walk in the meadow. Leaving this exemplar thinking, on a broader lever, these considerations suggest two things: a switch from habitual towards goal-directed movement can be established suddenly and to a certain extent as a voluntary act. Second, the transition between goal-directed and habitual behavior reflects rather a continuum than a strict dichotomy. Transitions between both extremes are possible in both direction, however there is a asymmetry of transition. The transition from goal-directed to habitual behavior is strenuous and depends

on (reward) learning. In contrast, by offering novel environmental cues, a sudden transition from habitual to goal-directed movement can be established almost instantaneously.

1.4 Habits as Action Sequences

Assuming that a certain task can be both goal-directed or habitual (depending on the setting), over-learned behavior cannot be defined imperatively based on devaluation in a model-free reinforcement model. Dezfouli and Balleine [50, 51, 52] offer an interesting alternative for formalizing goal-directed and habitual behavior. The authors propose that goal-directed actions involve sequential higher lever (cognitive) decisions that are implemented on previously acquired skills. Thus, this form of decision-making is not primarily guided by encoding the relationship between actions and their consequences (see also [53] for a cmprehensive review on decision making and basal ganglia function). However, after sufficient learning goal-directed behavior will become automatic. While in reinforcement learning habits are defined as behavior with insensitivity to outcome, Dezfouli proposed that habits are rather a concentration of actions executed together to form actions sequences, an idea that is also implemented in theory of event coding for sequential actions [54]. In a theoretical approach, the authors show that the formation of action sequences are sufficient to explain devaluation effects in habitual behavior without explicitly depending on a reinforcement model [54].

Using this 'reverse' approach (from motor output in variable environments), a direct comparison between analogous motor control in different settings is possible. Instead of providing different environments and studying the difference in motor behavior, one can also study identical behavior in a variable environment.

1.5 Electrophysiology of the Basal Ganglia

In the previous sections, a theoretical and neuroanatomical framework for a dichotomous representation of goals and habits in the brain was developed. But how is the proposed behavioral segregation represented and implemented on a neuronal (electrophysiological) level in humans? In general, beta-oscillatory activity in the basal ganglia play a predominant role in the control and modulation of motor activity. Beta-oscillations in the subthalamic nucleus (STN) are exceptionally well studied in Parkinson patients and animal models [55]. Many authors have shown that beta oscillations are critical for the generation and persistence of the Parkinsonian state: Subthalamic beta-power is pathologically increased in PD patients [56, 57, 58, 22, 21], a reduction of signal power in the beta-band correlates with clinical improvement [59, 60]. Furthermore, both the administration of levodopa [61] and high-frequency deep brain stimulation (DBS) of the STN [62, 60] lead to a suppression of resting beta-synchronicity, and stability in the beta-band has been correlated with severity of motor impairment [63, 64]. Conversely, the suppression of beta-activity prior to movement initiation in event-related tasks is necessary for motor initiation. In summary, these studies provide compelling

evidence that beta-oscillations within the basal ganglia are movement inhibitory [65, 58, 66, 67] and during ongoing movement, beta oscillatory activity must be suppressed.

Little is known however on the role of beta oscillation within the framework of goal-direced and habitual behavior. Some authors showed a link between external behavioral cues and event-related beta-desynchronization in the basal ganglia [68, 69], whereas others reported increased beta-power after salient cues in non-human primates [70]. Brown and co-workers found evidence for low frequency oscillations in the subthalamic nucleus to be modulated during decision making [71]. In a similar vein, however based on single neuron recordings, rodent experiments show changing striatal spiking patterns depending on the behaviour characteristic of habit learning [72]. Nevertheless, the functional segregation of motor control within cortico-basal ganglia loops between habitual and goal-directed motor control strongly suggests that distinct neuronal networks are recruited for different motor behaviors. From a behavioral perspective, it is important to notice, that despite the universal impairment of motor execution in PD, the context of motor initiation severely modulates motor performance: For instance, motor function can be drastically improved in PD patients by providing salient visual or auditive cues. [73, 74, 75] As an explanation for this effect, Redgrave and co-workers [1] proposed that in the Parkinsonian state, control of habitual behavior is more severely impaired than goal-directed behavior, resulting in the progressive reliance on goal-directed motor control. [1, 74] If this hypothesis holds true, the proposed complementary networks should also have a direct electrophysiological correlate in subcortical as well as cortical areas. Striatal neurons have been proposed by several authors as an important structure regulating the decision process between goal-directed and habitual behavior[76, 77, 39, 78, 79, 80, 81], suggesting a functional segregation also in the basal ganglia [82]. However, the role of the subthalamic nucleus (that is tightly connected to the striatal input) is less investigated [83]. Considering the outstanding role of subthalamic beta-oscillations in movement control, we specifically investigated in a series of paradigms whether beta-activity in the basal ganglia is modulated by the current mode of motor control (e.g. model free versus model based motor control). Specifically, we hypothesize that habitual (model-free) behavior is translated to reduced beta oscillatory activity in the basal ganglia. This monograph includes three independent studies on motor control in Parkinson patients. In a comparative approach, we set out to find electrophysiological correlates of the proposed dichotomy by applying the introduced theoretical model (Figure 3) in all motor paradigms.

This monograph aims at a discussion of motor behavior and its electrophysiological representation in a comparative approach in different settings by means of the introduced theoretical framework for motor control. All included studies aimed at comparing motor control in varying experimental setups. For example, to study voluntary finger movements, we established a paradigm for direct comparison between self-paced and cued motor control with identical motor output. In a similar vein, we studied electrophysiology of adaptive

and non-adaptive grip force control in simple tapping or shaking tasks. And we finally compared (voluntary) motor control during wakefulness and movement during REM sleep (where it is virtually impossible to distinguish between goal directed and habitual motor control). These approaches are different on many levels, but they share the characteristic of an analogous motor output (e.g. finger tapping, or pressing a device), but in changed environmental circumstances. This approach has the advantage that identical motor behavior can be studied in comparative task using different cognitive strategies. In contrast, the switch from habitual to goal directed movement is usually accompanied by a change of motor behavior (e.g. increased speed and accuracy). With regard to electrophysiology, the proper control for motor output is important, because speed or movement amplitude might cause additional changes in the studied motor networks.

2 Methods

2.1 General experimental approach

To establish a link between motor behavior and its central electrophysiological correlates, a simultaneous recording of motor control and electrophysiological signalling must be implemented. Whereas cortical activity is readily accessible through scalp EEG, subcortical structures (e.g. the basal ganglia) are not represented in the surface EEG. Thus, intracranial recordings from motor subcortical structures are mandatory to study motor control on a network level. In a subgroup of patients with Parkinson disease undergoing deep brain stimulation (DBS) in the subthalamic nucleus (STN), it is possible to access local field potentials through the implanted deep brain electrodes for few days post-operatively. To test our hypotheses, we therefore recruited PD patients scheduled for deep brain stimulation and measured EEG signals from scalp electrodes and subthalamic local field potentials (LFPs) from temporarily externalized DBS wires, while the patients were instructed to perform certain motor tasks. All studies discussed in this manuscript share this general approach of a trifold simultaneous measurement (EEG and LFP in correlation to motor output) as illustrated in Figure 2: Brain signals from the basal ganglia (subthalamic nucleus) are recorded from implanted DBS wires, EEG is measured from the scalp over various positions. In addition, various sensors have been used to access motor behavior. For the three presented studies we used touch sensors, grip force sensors or surface EMG for measuring motor output. The good time resolution of electrophysiological measures (scalp EEG, intracranial LFP) and the motor sensors allowed for an accurate time-locked measurement and correlation of movement and electrophysiological recordings.

The local field potential was recorded from all four contacts within both STN of each patient (sampling rate 200 Hz). Simultaneously, we recorded scalp EEG from a 12-channel subset of the 10-20 system at the fronto-polar (Fp1/Fp2), frontal (F3/F4), central (C3/C4), occipital (O1/O2) and midline (Fpz/Fz/Cz/Oz) electrode sites (sampling rate 200Hz). Time series data from the motion sensors was recorded on separate devices and synchronized by use of a differential TTL (transistor-transistor-logic) pulse.

2.2 Study Population

We included patients with Parkinson disease undergoing bilateral DBS lead implantation into the STN (Model 3389, Medtronic Neurological Division, Minneapolis, MN, USA) for all studies. DBS leads were implanted after MRI-based direct targeting of the STN. Accurate implantation of the leads within the STN was intra-operatively verified by micro-electrode recordings, clinical response upon intra-operative stimulation, and post-operative imaging. Invasive recordings in all three studies were performed on the second postoperative day in L-Dopa OFF and DBS OFF state, prior to connecting the leads to the subcutaneously implanted stimulation device. We excluded patients that were unable to be in L-Dopa OFF, had severe

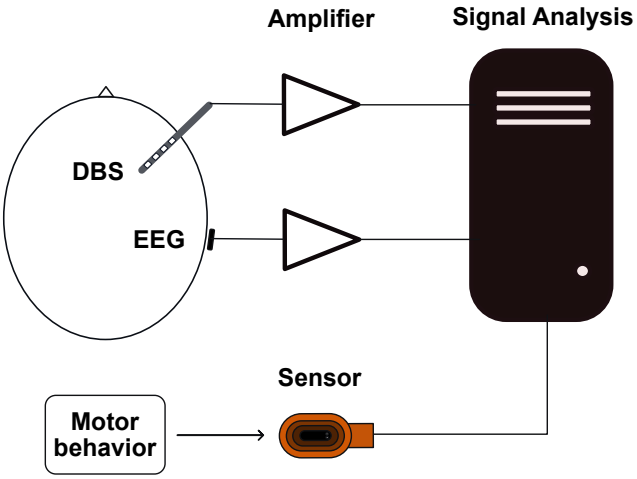

Figure 2: Experimental Setup: Local field potentials are measured through implanted deep brain electrodes (DBS), EEG is measured from surface electrodes and motor output is monitored by use of customized movement sensors.

dyskinesia. Decisions on patient selection and surgical procedures were not affected by this study and exclusively based on clinical grounds. All studies were approved by the local ethics committee and all patients gave informed written consent prior to study participation[22, 23, 21] .

2.3 Data post-processing

2.3.1 Spectral analysis

To investigate frequency specific changes of the raw EEG and LFP signal, the power spectral density (PSD) was calculated using the Welch periodogram approach for all conditions (Window size 1000 ms, non-overlapping Hanning window) as follows: First, for each epoch, the power spectral density function is estimated by calculating the squared amplitude of its fast Fourier transformation [84]

$$F(f) = \int_{-\infty}^{\infty} s(t) e^{-2\pi s t} dt \tag{1}$$

For a discrete signal of length T (defined in the period $[-T/2, +T/2]$, it can be shown that the squared amplitude of the Fourier transform can be taken as an approximation of the power spectral density (PSD) of the original signal for sufficiently large epochs.

$$PSD(f) \sim \frac{1}{T}|F(f)|^2, \; for\, T \to \infty \tag{2}$$

Average spectral power for an EEG or LFP raw signal within an specific frequency band can then be calculated from the PSD integration (or in the discrete case summation) of the PSD within predefined frequencies.

$$\beta - Power(13 - 35Hz) = \int_{f_a=13}^{f_b=35} PSD(f) \sim \sum_{i=n}^{i=m} PSD'(f_i) \tag{3}$$

For PSD' referring to the discrete power spectral density with $f_n \sim f_a$ and $f_m \sim f_b$, with n and m as discrete boundaries of the relevant spectral band.

2.3.2 Event related potentials

For the analysis of event related potentials (ERP), the electrophysiological raw signals must be processed with a higher temporal resolution, because time-locked changes of EEG/LFP time series are expected within 10-100ms before and 500ms after a motor response, whereas PSD estimates spectral density in a time window of at least 1000ms. The raw signal ($S_{raw}(t)$) is therefore first band-pass filtered in the time-domain without loss of temporal resolution. For the band-pass filtered signal $S_{filt}(t)$ the ERP is then calculated by back-averaging the raw signal based on the specified (motor) events. We then calculated time-frequency representations of the patient-specific band around each event using Stockwell transforms [85] . Each time-frequency representation underwent voice-normalization (i. e. normalization of the time-dependent power along each frequency by their average between -1 and -0.5 s). All normalized event time-frequency representations from one experiment were point-by-point averaged and subsequently summarized across the frequency-domain, thereby yielding a patient-specific band power modulation around the region of interest.

2.3.3 Phase locking value

To measure synchronicity between spatially separated brain region (e.g. EEG and LFP signals) over time, the phase locking value was calculated in an approach as described in [86]. Unlike coherence, PLV is not confounded by amplitude correlation and is therefore more reliable for the direct comparison of motor paradigms that elicit a markedly different power-modulation in the frequency of interest [87]. For estimation of synchronicity, first the Hilbert Transformation $H(S_{filt})$ of the filtered raw signal is calculated to access time-dependent phase information. The current complex phase of a time series is then derived by calculation the phase angle of $H(S_f)$ as $\phi(t) = angle(H(S_f))$, and $H(S_f) = R * e^{\phi}$. The average phase-locking value over N time-locked epochs $T_i = [t_i ... t_{i+1}]$ of two signals is then calculated as:

$$PLV(t) = \frac{1}{N}|\sum_{i=1}^{N} e^{i(\phi_1(T_i) - \phi_2(T_i))}| \tag{4}$$

3 Summary of the Studies

3.1 Study I: Adaptive grip force is modulated by subthalamic beta activity in Parkinson disease patients (Imbach et al)

In this study, we investigated the electrophysiological interplay between basal ganglia and cortical oscillations of adaptive grip force motor control. Adaptive grip force control refers to the fast and accurate sensomotor control of grip force in response to temporal changes of weight, frictional properties and acceleration of an object [88]. This extremely fast and accurate modus of motor control can be easily performed in a multi-task setting and requires little cognitive contribution and is therefore considered a highly overtrained (intrinsic or model-free) habitual task. In this study, adaptive grip force control was compared to voluntary repetitive pressing of the same object, as a more goal-directed task.

The core finding of this study was that for the same motor behavior (rhythmic compression and release of the device upon shaking or pressing), two distinct electrophysiological patterns were observed in the contralateral STN and the corresponding motor cortex. This finding indicates that the basal ganglia are involved in voluntary and adaptive precision grip force control, and that the type of motor behavior crucially affects the network processing of grip force adaptation in the basal ganglia.

Local field potentials in the subthalamic nucleus during temporal grip force adaptation showed a higher average suppression of beta oscillatory activity as compared to the voluntary task. During resting baseline condition, mean beta power spectral density within the STN showed a high beta band activity with a peak frequency around 20 Hz. To illustrate the beta-reduction across hands (N = 12), we normalized the spectral density measures during the motor tasks to the baseline condition. This normalization revealed that adaptive grip force suppresses beta oscillatory activity in a tonic (temporal stable) manner.

In contrast, the analysis of time-locked beta band desynchronization revealed a complementary pattern of less tonic beta suppression, but more temporally modulated ('phasic') time-locked desynchronization for both tasks: During the adaptive grip force task, beta power in the STN evolved in a single sinusoid desynchronization, which was indeed tightly time-locked to the phase of the grip force. During voluntary grip force control, STN beta ERP followed a two-phasic pattern. The two peaks of beta ERP occurred near the two inflection points of the grip force curve.

3.1.1 Beta connectivity in adaptive grip force

In terms of cortico-subcortical connectivity, we observed a marked desynchronization between motor cortex and basal ganglia during adaptive grip force. To compare the synchronization between STN and cortex across different tasks, we calculated the phase locking value between STN-LFP and all EEG electrode sites

within the high beta frequency band (20-35 Hz). The cortico-subcortical connectivity was high during the resting state and for voluntary motor control and was reduced during the more habitual adaptive grip force tasks. The reduction of phase locking (PLV) was most pronounced over the midline sites.

3.2 Study II: Electrophysiological evidence for alternative motor networks in REM sleep behavior disorder (Hackius et al)

This study aimed at investigating motor control during REM sleep in patients with REM sleep behavioral disorder (RBD). In strong contrast to severe bradykinesia during wakefulness in the OFF state, RBD patients often perform surprisingly fast movements that are usually in relation to dream content (enacted dreams) [89, 90]. RBD episodes typically show strong emotional or violent characteristics [91], but also non-violent behaviors such as laughing or singing have been reported [92, 93]. This context-specific activation of the motor system during REM sleep indicates that different motor networks are recruited for RBD movements versus voluntary motor control during wakefulness. In this study, we therefore set out to determine whether different motor networks are active during movements in RBD as compared to motor control in the waking state. To test this hypothesis, we recorded local field potentials in the subthalamic nucleus in patients with RBD and analyzed event related potentials upon movement initiation in REM sleep and in the waking state. Specifically, we asked whether the well known time-locked modulatory effect of beta oscillatory activity in the subthalamic nucleus is also observed during REM sleep movements. To test this hypothesis, we compared local field potentials in the STN and surface EEG during standardized voluntary movements in the waking state and sleep-related movements during REM sleep.

The main finding of this study was that sleep-related movements are not processed by the same cortico-basal ganglia network as movements in the waking state. Specifically, we observed beta oscillatory synchronization within the subthalamic nucleus during sleep related movements and cortico-basal ganglia desynchronization. We concluded from these findings that the well-known seemingly normal motor performance during REM sleep behavior disorder in PD patients might be generated by activating alternative motor networks for movement initiation.

3.2.1 Beta modulation in RBD movements

In agreement with previous studies, we found a significant beta desynchronization in the STN during movements in the off-medication waking state: In an event-related analysis, beta power was significantly lower as in a baseline condition 2.5 seconds after movement onset. In contrast, during movements in REM sleep, we observed marked beta synchronization with onset prior to the observed movement initiation. Beta synchronization reached a significant level 3.3 seconds prior to visually observable movements. Pairwise comparison

of beta power before and after movement onset revealed a significant decrease during voluntary movements in wakefulness, but in contrast an even more pronounced increase on beta oscillations during REM sleep movements.

3.2.2 Beta connectivity in RBD movements

To quantify cortico-subcortical coupling prior and during movements in wakefulness and REM sleep, we analyzed the phase locking value between the STN and the ipsilateral central EEG electrode. For movements during wakefulness, we found no relevant modulation of phase locking in the perimovement period 5 seconds before and after movement initiation. In contrast, during REM sleep, cortico-subthalamic synchronicity (as measured by phase locking) in the beta range was reduced after movement onset, indicating a significant decoupling of the basal ganglia from cortical neurons during RBD.

3.3 Study III: Functionally separated networks for self-paced and externally-cued motor execution in Parkinson's disease: evidence from deep brain recordings in humans (Bichsel et al.)

As an extension of the previous two studies, we implemented a novel comparative motor paradigm to investigate cued versus self-paced habitual motor behavior in awake PD patients. This paradigm was inspired by our previous findings showing a striking dichotomy of electrophysiological measures for seemingly identical motor output using more goal-directed (pressing) or more habitual (adaptive grip force) control. Furthermore, from a more anatomical perspective, evidence suggests that spatially segregated associative and sensorimotor cortico-basal ganglia circuits control for distinct neuronal networks that are recruited for different motor behaviors in PD. In this study we specifically investigated whether a shift from habitual to goal-directed control is reflected in a change of beta-activity on the basal ganglia level. We set out to test this hypothesis by measuring deep brain and surface neuronal activity in PD patients engaged in self-paced index finger tapping (habitual paradigm) and subsequent analogous externally-cued tapping (goal-directed paradigm) directed by acoustic cues. The key finding of this study was that only externally-cued movements induced a pro-kinetic event-related beta-desynchronization, whereas beta-oscillations were continuously suppressed during self-paced motor control. Beta phase-synchronicity analysis revealed inverse patterns of activation in two neuroanatomical networks proposed for controlling habitual and goal-directed movements, respectively. Therefore, this study provides electrophysiological evidence of different behavioral cortico-basal ganglia networks confirming the notion of distinctive motor control loops.

3.3.1 Beta modulation for self-paced versus cued movements

For spectral analysis, we first analyzed continuous beta suppression in both paradigms. We found that only self-paced tapping (as compared to resting state) affected the steady-state power spectral density of

the high-beta band, in terms of a significant desynchronization in the high-beta band during self-paced movements. In contrast, no significant changes where observed during externally-cued movements in any of the investigated beta-bands. In contrast to the tonic desynchronization in the STN-specific beta-band during self-paced motor control, we found time-locked event-related desynchronization exclusively during externally-cued movements. The maximal desynchronization was observed 200 ms after tap onset.

3.3.2 Beta connectivity for self-paced versus cued movements

Based on the assumption of distinct neuro-anatomical networks for cued and self-paced movements respectively, we investigated cortico-subthalamic coupling within two distinct cortico-subthalamic loops by calculating the phase locking value in each loop and for both motor behaviors separately. Qualitatively, we found higher synchronicity after tap onset in the sensorimotor loop during self-paced behavior. Conversely, during externally-cued movements, phase locking was higher in the associative loop. During the externally-cued paradigm, average phase synchronicity was found to be higher in the associative than in the sensorimotor loop.

4 Discussion

4.1 Different motor tasks in the behavioral model for motor control

The included studies all share the common methodological approach of comparing motor behavior with similar or identical motor output, but different type of motor activation (e.g. adaptive versus voluntary or REM sleep movements versus movements in wakefulness). The rigorous control for identical motor output allowed for a comprehensive comparison of the implemented motor tasks within each study, as summarized in the previous section. A comparison of the electrophysiological findings *between* theses studies is however less straightforward. For example, how are REM sleep related movements compared to cued tapping of the index finger in wakefulness?

A possible approach to this problem, is a comparison all studied motor tasks within the theoretical framework of implicit versus explicit motor control, as this approach allows for an interpretation of the electrophysiological findings not only within but also between studies with different experimental setup and implemented paradigms. The problem then remains to determine whether a certain motor behavior is executed relying on a more implicit or explicit internal model, which is discussed in the following section. Based on this working hypothesis, the categorization of the motor tasks and the electrophysiological properties (beta, STN-cortical activity) are summarized in Table 1.

Table 1: Tasks and Beta desynchronization within and across studies

paradigm - task	**model**	**beta response**	**STN-cortical connectivity**	**ref**
adaptive gripforce	implicit	tonic suppression	desynchronization	Imbach et al [21]
voluntary gripforce	explicit	phasic suppression	synchronization	
self-paced tapping	implicit	tonic suppression	desynchronization (STN-frontal)	Bichsel et al [22]
cued tapping	explicit	phasic suppression	synchronization (STN-frontal)	
REM sleep movements	implicit/limbic?	phasic increase	desynchronization	Hackius et al [23]
voluntary in wakefulness	explicit	phasic suppression	synchronization	

Gripforce Control By means of the multi-dimensional model for implicit versus explicit motor control, adaptive grip force control can be considered as implicit (habitual) behavior for several reasons. First, the speed of grip force adaptation and the accuracy of movements directly imply an implicit underlying model for motor output. In other words, a constant 'on-line' adaptation of gripfoce depending on oscillatory frequency or weight of the object would not be fast enough to allow for a smooth motor control. Also from a more behavioral perspective, adaptive gripforce is highly over-learned and can be performed with little cognitive contribution (multitasking during gripforce control is not problematic under normal circumstances). In comparison, voluntary pressing of the device is still a highly over-learned task, but it requires more cognitive effort, for example due to the generation of an internal cue for movement initiation. Multitasking might

still be possible, however more difficult in comparison . Within this model, voluntary repetitive pressing has therefore a more explicit (goal-directed) quality.

Self-paced versus Cued Motor Control Self-paced finger tapping in the study of Bichsel et al. is comparable to the self-paced pressing of the device in the gripforce task (see previous paragraph). Within the multidimensional model (Figure 1) this task combines aspects of both implicit (over-learned and fast), but also explicit motor control (generation of internal cues) and holds a middle position between both extremes (habitual and goal-directed control). Motor initiation based on visual or auditive cues, requires however more cognitive and attentive effort and be considered as strongly goal-directed: Participants are prone to errors (anticipation) and report higher difficulty for multitasking during this paradigm. Externally cued motor control is therefore considered as depending on a more explicit internal model (Figure 3).

Sleep Related Movements Sleep related movements are more difficult to classify within the implicit-versus-explicit model for motor control. In particular, movements during REM sleep are known to be usually related to dream content and represent motor output of enacted dreams. Whether this movement is voluntary (goal-directed) or depending on implicit motor control (habitual) is therefore intrinsically difficult to decide and only indirect arguments can be applied for answering this question. One characteristic feature of RBD movements is their relation to strong emotional (limbic) characteristic. Emotion-driven motor control in wakefulness is usually fast and requires little or no cognitive control. In this view, sleep related movements can be considered to be dependent more on a implicit (habitual) than on a explicit (goal-directed) control. In particular, the direct comparison of self-paced pressing of device during wakefulness with REM sleep movements (without certain conscious contribution) would support the interpretation of REM sleep movements being more dependent on implicit forward-models, although one might argue that limbic motor control is even generated by means of a separate unrelated motor network.

4.2 Meta-Analysis of Beta Oscillations and Cortico-subcortical Connectivity

The comparative analysis of beta oscillatory activity in the STN according to the hypothetical framework (implicit versus explicit motor control) reveals two consistent patterns of beta modulation, as illustrated in Figure 3. First, steady state beta activity is tonically lowered in all paradigms requiring a more implicit (habitual) model for motor output. Intuitively, a tonic ongoing desynchronization during implicit behavior is plausible, because well overtrained movements can be continued without repetitive input from cognitive or attentional networks. In other words, the required beta desynchronization for movement is initiated only once and continues in an all-or-nothing type of network recruiting. Conversely, the inverse pattern was found for more explicit (pressing or cued tapping) motor output: Tonic beta output is higher (movement inhibiting signalling), but the required beta reduction is implemented on a movement-by-movement basis and hence would lead to stronger event-related desynchronization in the subthalamic nucleus. Comparing

the motor tasks in the hypothetical framework as schematized in Figure 3, we indeed observed tonic beta-desynchronization in implicit movements, but phasic desynchronization in explicit behavior. The observation of different patterns of beta-modulation (time-locked desynchronization during goal-directed movement vs. tonic desynchronization during habitual behavior) provides electrophysiological support for distinct neuronal networks being recruited based on the movement task's nature. The neuronal signalling in the presumed networks apparently does not share the same pattern for movement activation. Interestingly, during goal-directed movement control, pathological beta-activity is repeatedly suppressed for every single movement (reflected by reduced event-related beta-power). Theoretical models support these findings by showing that tonic and phasic activity in midbrain neurons are competing systems in the regulation of goal-directed and habitual behavior respectively [94].

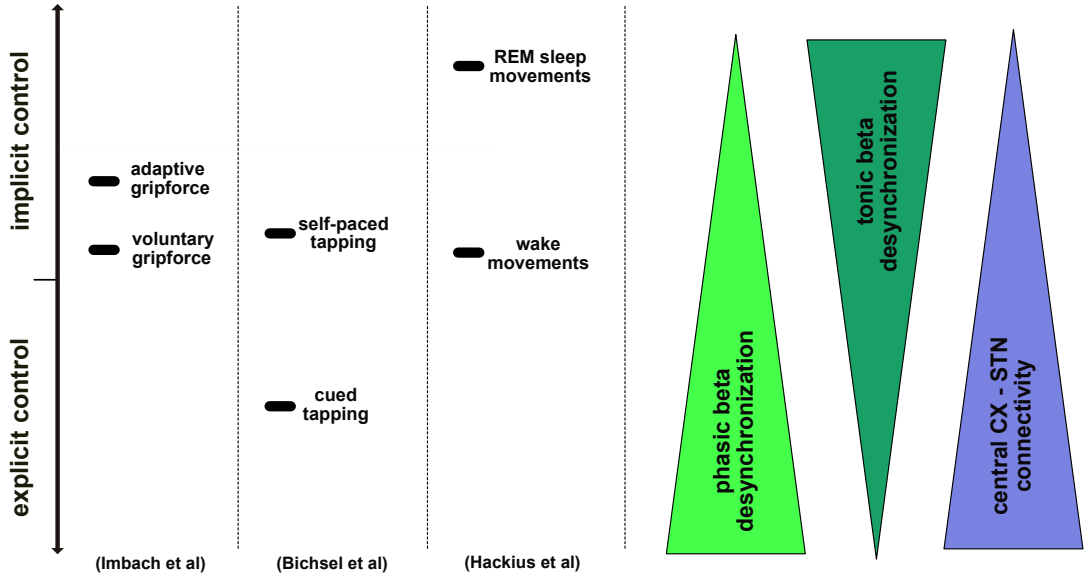

Figure 3: Schematic meta-analysis of beta oscillations and connectivity for different dichotomous motor tasks

4.3 Habits as action sequences

A further conclusion from the meta-analyzed data as presented in Figure 3 is that the seemingly dichotomous differentiation between goal-directed and habitual behavior is rather a relative distinction. For instance, self-paced movements during a grip force task are considered explicit, when compared to highly automatic (implicit) adaptive grip force control during a shaking task. Conversely, a very similar movement (self-paced tapping) is considered more habitual, when compared to explicit timed finger tapping based on visual cues. Intriguingly, beta desynchronization and phase locking follows this contextualization over various experimental setups and paradigms.

This relative or comparative dichotomy of goal-directed and habitual behavior depending on the circum-

stantial setup, in which a specific motor action is performed, challenges the concept of an *a priori* distinction between goal-directed or habitual behavior. However, as introduced by Balleine and Desfouli [52, 51] a habit can be defined as a newly formed joint sequence of previously single goal-directed 'sub-actions' generated by sufficient training. Applying this approach to the current studies, the motor tasks in the included studies can be analyzed in a comparative approach: For instance Study III [22] implements a task with ongoing GO/NO-GO condition that requires permanent goal-directed motor control, as the action sequence cannot be anticipated by the subject and therefore it is not possible to switch to habitual behavior in form of an action sequence. In contrast, self-paced tapping can be interpreted as an ongoing action sequence of continuous up- and down-ward movements. In terms of Dezfouli, a habit is formed by forming a sequence of goal-directed (single) movements [52, 51]. For this specific task, the propose that the whole sequence is initiated at movement onset only once and is continuously performed with little cognitive effort further on. Similarly, by shaking a device during the grip force task, the rapid sequence of press and release of the device is not performed in a goal-directed manner, but by implementing an adaptive sequence of press/release movements. This hierarchical sequencing of sub-goals within a higher level action sequence provides a possible basis for habitual grip force control.

Intriguingly, we found corresponding electrophysiological correlates for the proposed hierarchical model. Our analysis of beta oscillation in the subthalamic nucleus showed indeed that during more goal-directed movements, repetitive desynchronization were observed for every single movement. In other words, goal-directed movements are controlled in the basal ganglia on a 'one-by-one' level, as expected for explicit (goal-directed) behavior in the hypothetical model. This mode of action also guarantees that any movement can be individually 'started' or 'stopped'. A sudden change in the middle of an experiment (loss of cue, devaluation) would then instantly lead to change of behavior. In contrast, during habitual behavior (e.g. adaptive grip force and self-paced movements) the motor control can be thought of an action sequence: In agreement with this model, we observed movement-inducing beta desynchronization in a tonic manner: The individual beta desynchronization for goal-directed sub-movements are now replaced by a combined (ongoing) tonic beta-desynchronization that represents the motor *sequence* rather than the individual movements.

4.4 Implications for Parkinson disease

All of the included studies were performed in patients with Parkinson disease. PD patients suffer from progressive impairment of motor control caused by a loss of dopaminergic neurons in the basal ganglia. However, beyond the universal impairment of motor execution in PD, the context of motor initiation severely modulates motor performance: For instance, motor function can be drastically improved in PD patients by providing salient visual or auditive cues [75, 73, 95]. However, the reason for this striking dichotomy be-

tween spontaneous (implicit) and cued (explicit) movements is not fully understood. The reviewed data shows a comprehensive pattern of tonic beta desynchronization for implicit (habitual) movements and phasic desynchronization for explicit (goal-directed) motor control. Considering that baseline beta oscillatory activity is elevated in patients with PD, motor execution via explicit motor control (e.g. visual cues) might therefore provide a twofold benefit for PD patients. First, the explicit network might be less affected in terms of pathological beta-oscillations and therefore less beta-desynchronization is required for the same motor output. Second, the signaling architecture in the explicit network allows for a more efficient (time-locked) way of beta-desynchronization, hereby allowing for better motor performance at less cognitive effort. In implicit behavior, on the other hand, it is presumably more difficult to initiate and subsequently continue movement, which requires beta-oscillations in the STN to be continuously desynchronized, as only short interruptions, or pathological beta-bursts, are sufficient to abruptly terminate an ongoing habitual movement.

5 Conclusion

To provide a comparative discussion of the included studies, that are methodologically strongly related, but implemented different types of motor paradigms, a theoretical model-based framework was introduced. This model provided a working hypothesis to categorize the various motor paradigms in terms of implicit (habitual) or explicit (goal-directed) behavior. Interestingly, this cross comparative approach revealed distinct electrophysiological patters during implicit and explicit motor tasks within and between the discussed studies. These findings essentially supports the existence and recruitment of distinct neuronal networks during habitual and goal-directed behavior in PD patients in various experimental conditions and - on a more theoretical level - challenge the definition of habitual control exclusively by devaluation contingency as derived from animal models, but support the more general hypothesis that habits are computationally implemented as action sequences.

From a clinical perspective, these findings imply that habitual and goal-directed motor execution are controlled by segregated parallel networks. Therefore, motor performance may strongly depend on setting, training and implemented cognitive strategy. Now, the studied motor tasks also demonstrate that rapid transitions between different active motor networks are feasible. In other words implicit and explicit motor control may work in parallel, but environmental conditions favor one network over another. As in PD it has been hypothesized that implicit motor control is most severely affected, a possible strategy to ameliorate motor control could be to induce a network shift towards the less affected motor network (e.g. by providing tasks dependent cues). However, the electrophysiological data also revealed distinct patterns of network activity (phasic desynchronization for habitual tasks and tonic desynchronization for explicit tasks in all studies). To improve motor control in PD patients an alternative approach could be to modulate basal ganglia function for example by DBS in a selective rather than unspecific manner. Concretely, future studies could consider selective task-dependent deep brain stimulation depending on the actual implemented task: The patterns that were revealed in the discussed invasive recordings could provide a starting point for task-adaptive DBS. For example, during goal-directed motor performance a phasic (time-locked) stimulation might be more beneficial than the currently used tonic high frequency stimulation paradigm. Such an approach would however require an adaptive stimulative protocol with online knowledge of the currently performed task. Moreover, in a slightly different direction, one might consider to train patients towards a more pro-kinetic network activity. A possible approach in this direction could be to train PD patients to modulate their network activity using invasive neurofeedback techniques.

In conclusion, the analysis of motor behavior within a general theoretical model of implicit and explicit motor control provided a useful framework for the analysis of motor tasks revealing distinct electrophysiological activity patterns as a possible representation for alternative and functionally segregated motor networks in humans. Future studies might implement this insight to optimize neuromodulative therapeutical intervention in the treatment of PD patients.

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6 Appendix - Included Studies

6.1 Study I: Adaptive grip force is modulated by subthalamic beta activity in Parkinson disease patients (Imbach et al.)

6.2 Study II: Electrophysiological evidence for alternative motor networks in REM sleep behavior disorder (Hackius et al.)

6.3 Study III: Functionally separated networks for self-paced and externally-cued motor execution in Parkinson disease: evidence from deep brain recordings in humans (Bichsel et al.)

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Adaptive grip force is modulated by subthalamic beta activity in Parkinson's disease patients

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ABSTRACT

Introduction: Healthy subjects scale grip force to match the load defined by physical object properties such as weight, or dynamic properties such as inertia. Patients with Parkinson's disease (PD) show an elevated grip force in dynamic object handling, but temporal aspects of anticipatory grip force control are relatively preserved. In PD patients, beta frequency oscillatory activity in the basal ganglia is suppressed prior to externally paced movements. However, the role of the subthalamic nucleus (STN) in anticipatory grip force control is not known.
Methods: After implantation of deep brain stimulation (DBS) electrodes in the STN, PD patients performed adaptive and voluntary grip force tasks, while we recorded subthalamic local field potentials (LFP) and scalp EEG.
Results: During adaptive grip force control (Shake), we found event related desynchronization (ERD) in the beta frequency band, which was time-locked to the grip force. In contrast, during voluntary grip force control (Press) we recorded a biphasic ERD, corresponding to peak grip force and grip force release. Beta synchronization between STN and cortical EEG was reduced during adaptive grip force control.
Conclusion: The time-locked suppression of beta oscillatory activity in the STN is in line with previous reports of beta ERD prior to voluntary movements. Our results show that the STN is involved in anticipatory grip force control in PD patients. The difference in the phasic beta ERD between the two tasks and the reduction of cortico-subthalamic synchronization suggests that qualitatively different neuronal network states are involved in different grip force control tasks.

1. Introduction

Scaling and temporal adjustment of precision grip force is a highly efficient skill in everyday life. While grasping an object, healthy subjects precisely scale the applied grip force to match the load defined by physical object properties, such as weight and shape, as well as dynamic properties such as inertia (Prodoehl et al., 2009).

Neural implementation of precision grip force control is embedded in a complex network involving pre-motor cortical areas, the cerebellum and sub-cortical structures, particularly the basal ganglia (Nowak et al., 2007; Dafotakis et al., 2008; Prodoehl et al., 2009). Neuroimaging studies have shown that basal ganglia are involved in both predictive (dynamic) aspects of grip force control, as well as parameterization of grip force scaling (Vaillancourt et al., 2007; Prodoehl et al., 2008, 2009; Wasson et al., 2010).

In Parkinson's disease (PD) a distinction between dynamic grip force control and grip force scaling is observed: Whereas temporal aspects of dynamic grip force control are relatively preserved (Nowak and Hermsdörfer, 2002; Albert et al., 2010), grip force scaling is pathologically elevated in PD patients (Fellows et al., 1998). Direct evidence for the involvement of the subthalamic nucleus (STN) in grip force scaling has been obtained in PD patients treated by deep brain stimulation (DBS), where pathologically elevated peak grip force could be normalized by chronic DBS (Wenzelburger et al., 2002).

For temporal adaptation of precision grip force, the cerebellum is another key structure: It has been shown that patients with cerebellar disease suffer from impaired grip force control (Rost et al., 2005; Nowak et al., 2007). In this line, grip force adaptation relies on internal

Abbreviations: PD, Parkinson's disease; DBS, deep brain stimulation; STN, subthalamic nucleus; ERD, event related desynchronization; ERP, event related potentials.

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anticipatory models in the brain, which are mainly based in the cerebellum (Miall et al., 1993; Wolpert and Miall, 1996; Wolpert et al., 1998). The tight functional connections between basal ganglia and cerebellum (Hoshi et al., 2005; Bostan et al., 2010), suggest a dynamic interplay between the cerebellum and the basal ganglia in dynamic grip force control. While data from neuroimaging, anatomy and behavior point to an important role of basal ganglia networks in grip force control, the underlying neuronal activity is still unknown.

Various studies have demonstrated high beta power in the STN of PD patients (Brown et al., 2001) and the amount (Kühn et al., 2004; Pogosyan et al., 2010; Zaidel et al., 2010) and stability (Little et al., 2012) of beta activity in the STN correlates negatively with motor performance. The outstanding role of beta oscillations for bradykinesia has been demonstrated by inducing a frequency-specific impairment in a grip force task upon low-frequency stimulation in the STN of PD patients (Chen et al., 2011). Whereas beta activity in the basal ganglia may simply be an epiphenomenon of enhanced neuronal synchronicity during movement initiation, the suppression of beta activity before movement initiation in event-related tasks (Brown et al., 2001; Kühn et al., 2006; Oswal et al., 2012) provides evidence that dynamic changes in beta oscillations are critical for motor control *per se*. Extending this idea, dissociation of salient cues and actual motor execution supports the hypothesis that beta desynchronization prospectively modulates executive motor processing (Oswal et al., 2012; Gremel and Costa, 2013). To investigate prospective motor control, we examined how STN beta activity is modulated with adaptive grip force control during a shaking movement as compared to a control condition with voluntary grip-force initiation.

2. Methods

2.1. Patients and surgery

We included 6 PD patients who underwent DBS in the subthalamic nucleus (STN). Patients' demographic data and clinical details are summarized in Table 1. Bilateral DBS electrodes (Model 3389, Medtronic Neurological Division, Minneapolis, MN, USA) were implanted after MRI-based direct targeting of the STN (Bejjani et al., 2000). Intraoperatively, accurate implantation of the electrodes within the STN was verified by microelectrode recordings, followed by test stimulation to assess the clinical response, and by CT-imaging to reconstruct the effective electrode position (Schrader and Mehdorn, 2004). The data presented here were recorded on the second post-operative day at preoperative L-dopa levels (ON condition). Local field potentials (LFP) were recorded on temporarily externalized wires before implantation of the DBS impulse-generator. All patients gave informed written consent to participate in the study. The study was approved by the institutional ethics review board (*Kantonale Ethikkommission Zurich* KEK-ZH: 2012-0327).

2.2. Grip force recording

Adaptive grip force control during motor tasks was measured by a customized device. This device determines and records the applied grip force of the patient's fingers with an in-built force sensor and contains linear acceleration sensors for simultaneous registration of movement in three dimensions (Fig. 1A). In the case of oscillatory movements (e.g. shaking), force adaptation relies on an anticipatory internal model. Successful anticipatory grip force control is characterized by a matching of the applied grip force to the loading forces (mass + acceleration) of the device, which were generated by the movement. The device is cuboid ($60 \times 60 \times 40$ mm) and weighs 300 g (Fig. 1B) and emits a TTL pulse for synchronization with other data acquisition systems. To quantify the accuracy of the time-dependent grip-force adaptation, we calculated the correlation coefficient between grip force and loading force (Table 2) as a quantitative measure for the quality of grip force adaptation (Nowak and Hermsdörfer, 2005).

2.3. LFP and EEG recordings

The LFP was recorded from all contacts within both STN of each patient (sampling rate 200 Hz). Simultaneously, we recorded scalp EEG from a 12-channel subset of the 10–20 system at the fronto-polar (Fp1/Fp2), frontal (F3/F4), central (C3/C4), occipital (O1/O2) and midline (Fpz/Fz/Cz/Oz) electrode sites (Fig. 1C). The central midline electrode Cz was used as recording reference for EEG and LFP. As verified by post-operative reconstruction of the electrode position, the second lowest contact (Fig. 1D, Sarnthein et al., 2013) was located in the motor part of the STN in all patients and taken for further analysis. To reduce movement and electrode artifacts, we digitally re-referenced all signals to a Laplacian montage with weighted averages of the surrounding deep brain electrodes (for LFP channels) and surface electrodes (for EEG channels). This montage allowed for a significant reduction of the artifact level, but at the same time ensured the linear independence of cortical and LFP signals for the calculation of cortico-subthalamic synchronization.

2.4. Motor tasks

All experiments were performed in a sitting position. Patients grasped the measurement device with all fingers of one hand, while the other arm was in a resting position. To minimize interference with visual feedback, all experiments were performed with closed eyes.

For the shaking task (Shake), patients were instructed to shake the cube in a predefined manner, i.e. to perform consecutive point-to-point up- and downward movements in front of the trunk with an amplitude of about 20 cm. This shaking movement was self-paced, but patients were instructed to reach a frequency of approximately 2 Hz, if possible, depending on bradykinesia and rigor. After instruction of the patients and test-runs where necessary, we recorded a 90 s-epoch for each hand.

Two control tasks were performed: In a hold condition (Hold), the device was held steadily in one hand without movement to measure the 'resting state' background level of the STN and cortical EEG signal. For a pressing condition (Press), patients pressed rhythmically on the device in the same frequency as the arm was moved during the shaking task, but without moving the device itself. This task was introduced to control for *voluntary* self-paced grip-force initiation (Press), as compared to *anticipatory* grip force control adjusted by somatosensory feedback (Shake). By this experimental design we were able to compare two

Table 1
Demographic and clinical patient characteristics. UPDRS: Unified Parkinson's Disease Rating Scale, ON/OFF values of preoperative L-dopa challenge test; LED: levodopa equivalent dose at the time of recording.

ID	Age [y]	Gender	Parkinson type	Disease duration [y]	Hoehn–Yahr Scale	UPDRS III ON/OFF	LED [mg/d]
1	61	F	Rigid akinetic	9	2	12/24	850
2	63	M	Tremor dominant	12	2	16/55	1000
3	48	M	Young onset	10	2.5	11/53	500
4	47	M	Young onset	12	2	18/46	1000
5	73	M	Tremor dominant	10	2	18/37	1000
6	53	M	Rigid akinetic	14	2.5	28/52	2300

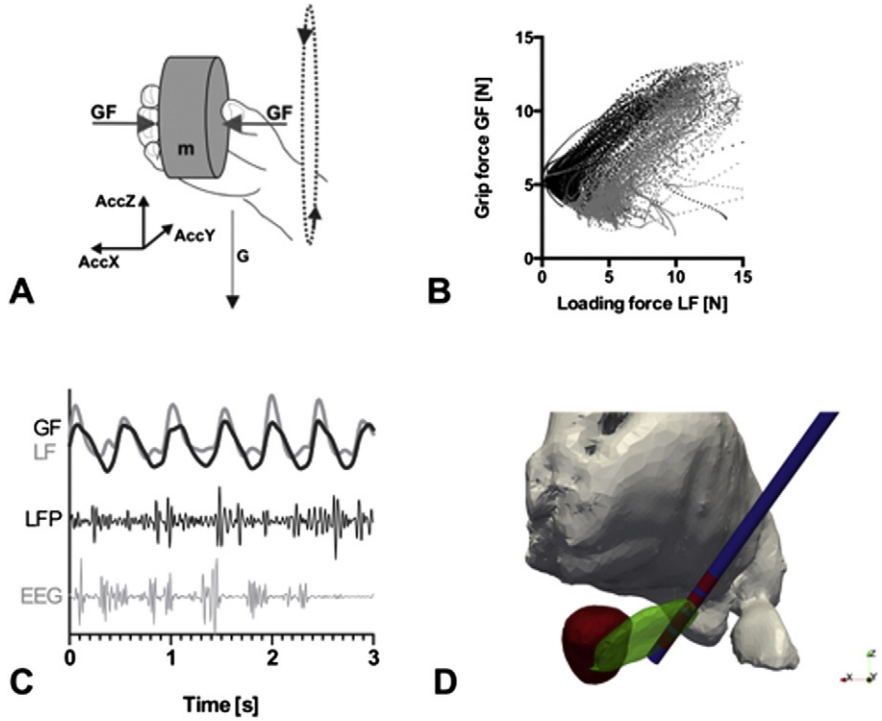

Fig. 1. Experimental setup. (A) Schematic plot of the measuring device for simultaneous acquisition of grip force (GF) and acceleration in 3 dimensions (AccZ, AccX, AccY). Acceleration in the Z-direction (AccZ) equals the loading force (LF). (B) Illustration of the correlation between grip force and loading force (i.e. acceleration in Z direction) for upwards (black) and downwards (gray) directed movement in one patient during the shaking task (C) behavioral data (grip force GF and loading force LF) and electrophysiological data (local field potentials LFP and surface EEG) were recorded simultaneously. (D) Projection of the reconstructed electrode position onto a 3D-Atlas (Sarnthein et al., 2013). The second lowest contact (red) of the electrode (blue) is located in the dorsal STN (green) and this signal was used for subsequent analyses. Red nucleus (red) and thalamus (gray).

movements with identical grip force (i.e. rhythmic contraction of the fingers in one hand), but presumably different central activating network states.

All subjects performed the tasks in the same sequence Hold–Shake–Press. Hold familiarized the subjects with the cube. In Shake, subjects discovered and trained their individual shaking frequency. Subjects then used this frequency in the self-paced Press condition (Fig. 2B).

To compare the motor output of the clinically more affected with the less affected side, we calculated the mean amplitude of the applied grip force for both hands during the motor tasks. To test for a disease specific impairment, we correlated the mean grip force amplitudes from both sides in all patients (N = 12 recordings, Fig. 2A). The mean frequencies of both movements (Press and Shake) were determined by spectral analysis of the grip force trace (Welch's periodogram; 2000 ms non-overlapping Hanning window). The peak frequency for Press was then correlated with the peak frequency of Shake (Fig. 2B).

The load force was calculated as the sum of weight (m × G), acting vertically to the grip surface, and the acceleration-dependent inertial loads in the vertical and sagittal directions (m × AccZ, m × AccY) (Rost et al., 2005).

Table 2
Correlation coefficients (Pearson's R) for grip force and loading force in fixed intervals of 250 ms during grip force release (upward movement) and grip force increase (downward movement).

Subject ID	GF increase	GF release
1	0.44	0.43
2	0.74	0.58
3	0.93	0.94
4	0.49	0.58
5	0.73	0.68
6	0.66	0.84
Median	0.70	0.63

2.5. Spectral power

We computed the power spectral density (PSD) of the LFP with Welch's periodogram on the full 90 s epoch for all conditions (1000 ms non-overlapping Hanning window). For all consecutive analyses of the LFP signals, we correlated the LFP recording with the behavioral data from the contralateral hand in all patients.

The event-related analysis was conducted following the approach by Kühn and coworkers (Kühn, 2004). For Shake and Press, the maximal grip force of each cycle was used as a trigger event. Event-related potentials (ERP) were calculated for 250 ms before and after this event: the LFP signal was beta-bandpass-filtered (13–35 Hz), amplitude-squared and averaged across all events within one subject. To get a comparable measure of time-dependent beta activity, the normalized cumulative sum (Kühn, 2004) of the beta ERP was calculated. This measure provides ascending slopes during phases of beta-synchronization (high average beta activity), and descending slopes for beta-desynchronizing states (low average beta activity). The resulting time-dependent signals were averaged across subjects and hemispheres. Confidence limits are given as a standard error of the mean (SEM) for all averaged spectra and ERP (N = 12).

2.6. Synchronization measures

The synchronization between EEG and LFP was first estimated by magnitude squared coherence (MSC) between the LFP and the ipsilateral central EEG-derivation (1000 ms non-overlapping Hamming window). The magnitude squared coherence MSC_{xy} for two signals, x and y, is equal to the average cross-power spectrum P_{xy} normalized by the averaged power spectra of the signals $MSC_{xy} = |P_{xy}|^2 / (P_{xx}P_{yy})$. Coherence assesses the strength of the linear relationship between two signals at every frequency f, and its value lies between 0 and 100%. It estimates the degree to which phases and amplitudes are dispersed at the

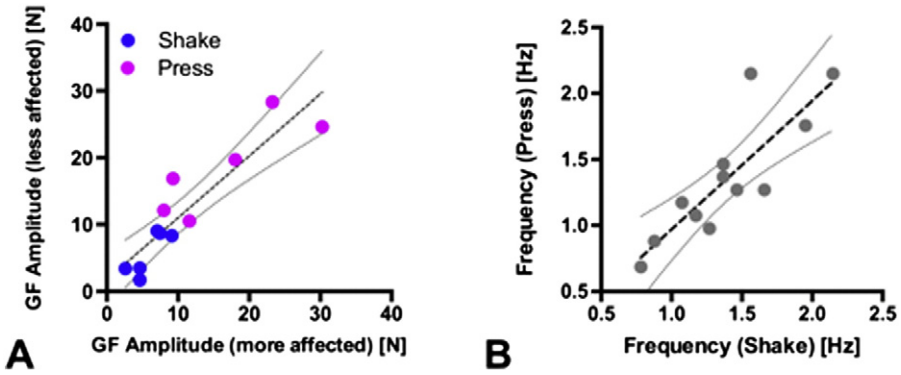

Fig. 2. Grip force amplitude and frequency during motor tasks. (A) Analysis of the mean GF amplitude for the more affected, versus the less effected hand in all patients showed a significant correlation, indicating that GF amplitudes did not differ between both extremities within subjects (Slope: 0.92 ± 0.13, $R^2 = 0.82$, $p < 0.005$, $N = 12$). Across tasks, the mean grip force was higher during Press (magenta, 17.7 ± 7.2 N) than during Shake (blue, 5.8 ± 2.7 N, $p < 0.005$ paired t-test). (B) The mean movement frequency of Shake and Press was highly correlated across hands (Slope: 0.97 ± 0.19, $R^2 = 0.71$, $p < 0.005$, $N = 12$, dotted lines: 95% confidence intervals for linear correlation).

frequency of interest. $MSC_{xy} = 0$ means phases and amplitudes are randomly dispersed among all epochs. Signals are perfectly coherent ($MSC_{xy} = 100\%$) at a given frequency when they have both a constant phase difference φ and constant amplitude ratio over the time considered. In this case, phases of signals *x* and *y* are identical in all epochs (i.e. the two signals are completely phase-locked at this frequency). The time lag between EEG and LFP was estimated on the basis of the phase differences φ of the cross-spectral power as calculated by Welch's averaged periodogram (1000 ms non-overlapping Hanning window).

To compare EEG–LFP synchronization across different motor behaviors, we then calculated the phase locking value (PLV) (Tass et al., 1998). We chose the PLV because – as opposed to MSC – it is independent of signal amplitude and is therefore more reliable for the direct comparison of different motor tasks, which elicit markedly different power spectral densities in the beta band. Taking the frequency range where the MSC differed most across motor tasks, we subsequently calculated the PLV in the high beta band (20–35 Hz).

2.7. Statistics

Motor output was analyzed with code written in LabView (Nowak and Hermsdörfer, 2005). Spectral analyses were performed with custom scripts written in MatLab (http://www.mathworks.com). For the calculation of the PLV we used the Neurophysiological Biomarker Toolbox (Hardstone et al., 2012). We used GraphPad Prism (http://www.graphpad.com) for statistical analyses and to create the figures. Parametric and non-parametric tests were used as applicable. Statistical significance was established at $p < 0.05$.

3. Results

3.1. Motor output

To investigate the time-dependent adaptation of grip force during the shaking task, we analyzed the correlation between loading force and applied grip force as illustrated in Fig. 1B. The correlation coefficients in the first (grip force increase) and second (grip force release) phase of the movement did not differ significantly (Table 2). The motor output of grip force adaptation was thus the same for both tasks.

Grip force amplitude of the clinically more affected and the clinically less affected hand were highly correlated (Slope: 0.92 ± 0.13, $R^2 = 0.82$, $p < 0.005$, Fig. 2A), indicating that the patients were able to perform the grip force tasks with each hand at the same precision. Across tasks, the mean amplitude was significantly higher during Press than in Shake ($p < 0.005$, Fig. 2A).

The mean movement frequency during Shake and Press showed a highly significant correlation, indicating that the movement frequencies were stable within one hand (Slope: 0.97 ± 0.19, $R^2 = 0.71$, $p < 0.005$, Fig. 2B).

3.2. Beta power in STN

During the Hold condition, the mean PSD of the STN traces showed a high beta band activity with a peak frequency around 20 Hz (Fig. 3A). To illustrate the PSD-reduction across hands ($N = 12$), we normalized the PSD of Shake and Press by the PSD of Hold (Fig. 3B). This revealed some changes in beta during Press and a pronounced beta desynchronization during Shake.

3.3. Event related beta desynchronization in STN

To investigate the time course of beta event related potentials (ERP), we defined the maximal grip force of each movement cycle as the trigger event. During Shake, the beta power in STN evolved in a sine wave, which was indeed tightly time-locked to the phase of the grip force (Fig. 4A). The maximal beta desynchronization occurred at the time point when the grip force curve had its maximal slope, i.e. at the inflection point preceding maximal grip force (downward movement). The time course of STN beta ERP during Shake can thus be modeled as the derivative of the applied grip force, $d(\cos \omega t) / dt = -\sin \omega t$ (Fig. 4C). In other words: The incremental change of force is proportional to the change in beta ERP.

During Press, STN beta ERP followed a two-phasic pattern. The two peaks of beta ERP occurred near the two inflection points of the grip force curve, one preceding maximal grip force and one preceding minimal grip force (Fig. 4B). The first peak of Press has the same amplitude and time-lag (−0.15 s) as the peak in Shake. In Fig. 4D, modeling the time course of STN beta power by $(-\cos \omega t - \cos 2\omega t) / 2$ gives 0 at $t = -\pi$ and −1 at $t = 0$ zero with the periodicity and the symmetry of the data in Fig. 4B. The model function is proportional to a superposition of the second order derivatives $d(\cos \omega t)^2 / dt^2$ at the fundamental frequency (ω) and the first harmonic (2ω).

3.4. Synchronization between LFP and scalp EEG

Fig. 5A shows the MSC between LFP in the STN and the ipsilateral central EEG (C3 or C4, respectively) averaged across all subjects for all task conditions. The MSC with its broad beta peak (20–35 Hz) for Hold and Press resembles the PSD (Fig. 3A). As in the PSD, this MSC peak was reduced during Shake. Complementary to MSC, the time lag between LFP and EEG can be estimated from the phase spectrum. The time lags for individual patients are given in Table 3 (median 15 ms, SEM 5 ms). The averaged phase spectrum is given in Fig. 5B with mean beta phase lag −1.3 rad. Scalp EEG leads the subthalamic LFP.

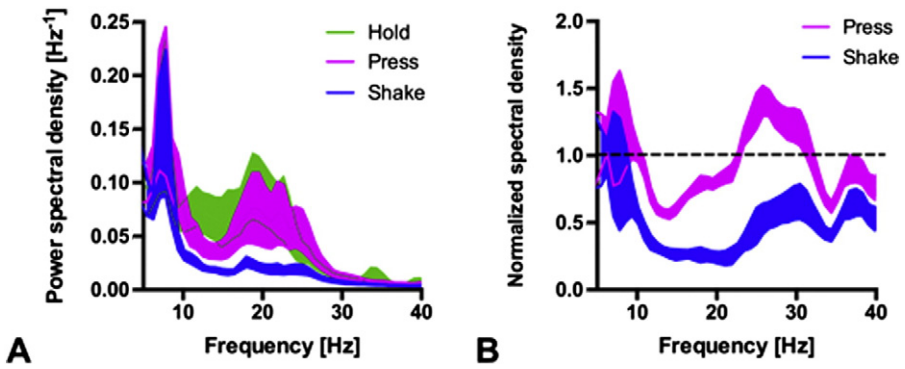

Fig. 3. Task-specific beta oscillatory activity. (A) The power spectral density (PSD) averaged across hands (N = 12) showed a broad beta peak during Hold (ribbon: SEM). (B) Normalizing the PSD of Shake and Press by the PSD of Hold reveals some beta decrease for Press and a pronounced beta desynchronization during Shake.

To compare the synchronization between STN and cortex across different tasks, we calculated the PLV between LFP and all EEG electrode sites (Fig. 6A). Guided by the frequency range of high MSC, we calculated the PLV in the 20–35 Hz high beta band. The PLV was high during Hold and Press and was reduced during Shake. The reduction of PLV was most pronounced over the midline sites (Fig. 6B).

4. Discussion

4.1. Adaptive grip force control involves STN activity

We investigated the role of beta oscillatory activity in the STN during adaptive grip force tasks in PD patients. The core finding was that the LFP in the STN during temporal grip force adaptation showed a time-locked beta band desynchronization in all subjects and hands. The LFP spectra showed marked differences between two movement tasks (Shake vs. Press), although the behavioral motor output (the temporal adaptation of precision grip force) was the same in both tasks (Fig. 4). In other words: for the same motor behavior (rhythmic compression and release of the device upon shaking or pressing), two distinct electrophysiological patterns were observed in the contralateral STN. This finding indicates that the basal ganglia are involved in voluntary and adaptive precision grip force control, and that the type of motor behavior crucially affects the network processing of grip force adaptation in the basal ganglia.

In agreement with previous studies in PD patients, ongoing movement desynchronized STN beta power compared to the resting state (Hold). The desynchronization was more pronounced for the habitual grip force task (Shake, Fig. 4A) as compared to the voluntary grip force task (Press, Fig. 4B). Similarly, cortico-subthalamic synchronization (MSC and PLV) was markedly reduced during Shake (Figs. 5 and 6). This suggests that a habitual, internalized and over-learned motor task like shaking the device is controlled with less cortical involvement.

4.2. PD patients are not impaired in the Shake task

For the Shake task, PD patients' behavior is comparable to that of healthy controls as has been demonstrated previously by the high correlation of adaptive grip force to a temporal changing loading force (Nowak and Hermsdörfer, 2002; Albert et al., 2010). Also in our patient group,

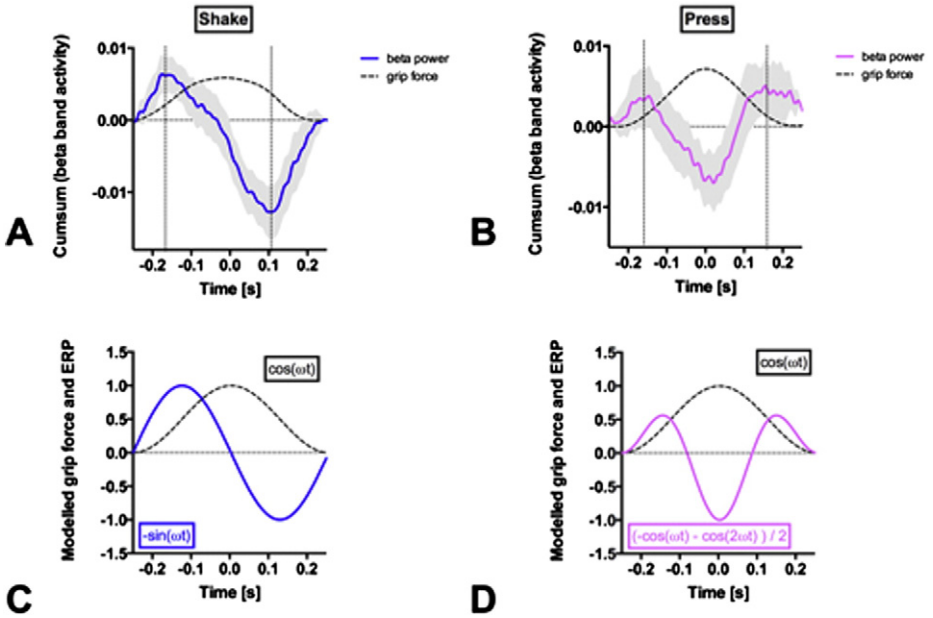

Fig. 4. Grip force and beta ERP in STN. (A) Shaking task traces. The averaged grip force (dashed line) increases towards t = 0 while subjects move the device downwards. For averaging, grip force curves were aligned at maximal grip force at t = 0 (reversal point). The averaged grip force curve turns to the right (second derivative <0) between infliction points (vertical dashed lines) and beta ERP (blue line; gray ribbon: SEM for N = 12) decreases monotonically. (B) Pressing task traces. While the grip force evolves as that during Shake, the beta ERP (magenta line; gray ribbon: SEM for N = 12) follows a biphasic pattern. (C) Modeling Shake traces. The grip force trace follows cos ωt with frequency ω. The time course of STN beta ERP is the derivative of the applied grip force, d(cos ωt) / dt = −sin ωt. (D) Modeling Press traces. The grip force trace follows cos ωt as that during Shake. The time course of STN beta ERP (−cos ωt − cos 2ωt) / 2 is proportional to a superposition of the second order derivatives $d(\cos \omega t)^2 / dt^2$ at the fundamental frequency (ω) and the first harmonic (2ω).

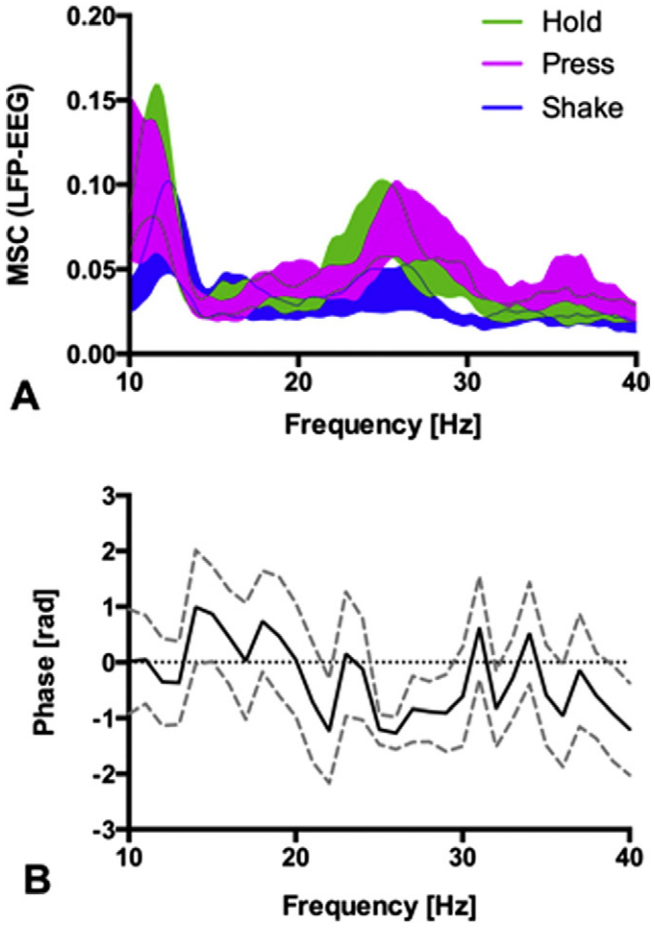

Fig. 5. Coherence and phase lag between LFP and EEG. (A) Magnitude-squared coherence (MSC) during Shake (mean ± SEM, N = 12) is lower than that during Hold and Press in high beta (20–35 Hz). (B) The phase spectrum (mean ± SEM, N = 12) is negative in the high beta range (phase lag = −1.3 rad). Scalp EEG leads the LFP.

motor output and electrophysiological characteristics were the same for the more affected and the less affected brain hemisphere. This suggests that the observed dynamic STN modulation might be representative of any STN including a healthy one.

4.3. Adaptive grip force control relies on an internal model

From a computational perspective, we can interpret these findings in the light of the proposed forward models during cerebellar-driven precision grip force tasks. Currently, in this field there is still very little behavioral and electrophysiological data in humans regarding the proposed interplay between the basal ganglia and the cerebellum. Only two studies provide evidence that the anatomical connections between the cerebellum and the basal ganglia are also functionally relevant (Hoshi et al., 2005; Bostan et al., 2010). Based on the theoretical framework of internal forward models for cerebellar-generated movements (Wolpert and Miall, 1996; Wolpert et al., 1998), we propose that the two examined tasks in this study (Shake and Press) are processed by different neuroanatomical networks.

Table 3
Beta peak frequency, magnitude squared coherence (MSC), peak phase lag, and estimated time lag. In all subjects (N = 6), values of both hemispheres were averaged.

ID	Frequency [Hz]	MSC	Phase [rad]	Time lag [ms]
1	16	0.07	−0.6	−6
2	22	0.07	−2.8	−21
3	27	0.12	−1.2	−10
4	20	0.02	−1.9	−15
5	21	0.01	−1.9	−15
6	25	0.17	−3.1	−20
Median	**21.5**	**0.1**	**−1.9**	**−15**

During the Shake movement sequence, the downward movement is triggered voluntarily. There is only one beta ERD per movement cycle, suggesting that only the downward movement is initiated voluntarily. The upward movement, as a rebound, proceeds without STN beta ERD in this habitual movement sequence. The Shake movement sequence is highly habitual with little cortical involvement, as evidenced by the low cortico-subthalamic synchronization (Figs. 5 and 6). Adapting the grip force does not consume conscious resources but is rather derived from an internal model, which involves the cerebellum. In the STN, the instantiation of the internal model is reflected in the mathematical first derivative of the grip force $d(\cos \omega t) / dt$ (Fig. 4C). The subthalamic beta ERP thus represents not the force itself but rather the incremental change of force. This supports the role of the basal ganglia as a dynamic relay in fine-tuning of motor execution.

In the Press task, both the grip force initiation and the grip force release are triggered voluntarily. We found cortico-subthalamic synchronization as high as during resting (Hold, Figs. 5 and 6) and two peaks of STN beta ERP in the movement cycle. The two peaks are reflected in the mathematical harmonic (2ω) and the second order derivative $d(\cos \omega t)^2/dt^2$ in our model of the beta time course (Fig. 4D).

4.4. Anatomical considerations

On a network level, the reduced coherence during the shaking task can be interpreted in light of the proposed neuroanatomical distinction between grip force scaling and temporal grip force control in anterior and posterior basal ganglia nuclei: for the voluntary Press task we found higher cortico-STN coherence, indicating that this task is embedded in a cortico-basal ganglia network controlling for grip force *parameterization*. On the other hand, *adaptive* grip force control is mediated predominantly through anterior basal ganglia nuclei and accordingly cortico-STN coherence is diminished during Shake. High cortico-STN connectivity during Press may also point to an involvement of the hyperdirect pathway in voluntary grip force control. In this light, our findings suggest that the hyperdirect pathway is predominantly activated during voluntary grip force control and reduced in adaptive grip force control. Furthermore, the hyperdirect pathway has been proposed to play a role in sustaining beta oscillatory activity in the STN (Jenkinson and Brown, 2011; Moran et al., 2011). Accordingly, we found higher power spectral density in the beta band during the pressing task, supporting the argument that an (over-)active hyperdirect pathway may cause elevated beta band activity in the STN. Finally, on a behavioral level, we observed significantly higher grip force amplitudes during the pressing task as compared to the shaking task, which could be caused by inhibiting signals from the hyperdirect pathway during voluntary grip force control.

4.5. Implications for the understanding of dysfunctions in PD patients

STN beta ERP showed a different time course in the two movement tasks. In Shake, there was one peak of beta ERP prior to maximal grip force. In Press there were two peaks, one prior to maximal and one prior to minimal grip force. These temporal changes of synchronicity in the basal ganglia provide complementary information in the understanding of pathological network activity in PD patients (Little et al., 2012).

As a clinical observation, habitual movement control is typically more affected in PD patients. Assuming that the baseline beta oscillatory activity (like Hold) is pathologically elevated in PD patients, a higher amount of beta desynchronization is needed to initiate and maintain habitual movement (like Shake), which is prominently controlled by sub-cortical networks. Clinical studies showed a prolonged and excessive grip force adaptation after motor engagement (Wenzelburger et al.,

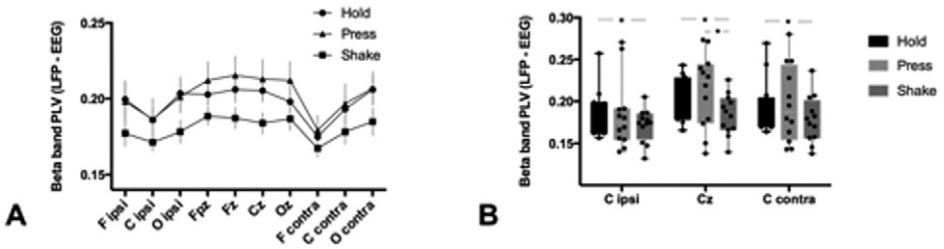

Fig. 6. Phase locking (PLV) between LFP and EEG in high beta (20–35 Hz). (A) The PLV during Shake is lower than that during Hold and Press for all scalp electrode sites (ipsi: ipsilateral to STN; contra: contralateral to STN). (B) For central scalp electrodes, the PLV is lowest during Shake in all N = 12 recordings (* = $p < 0.05$, paired Wilcoxon test).

2002). This is reflected by the observation that not only movement initiation is impaired in PD patients (as seen, e.g. in freezing of gait), but also termination of an ongoing movement is disturbed, resulting in involuntary prolonged movements (e.g. festinating gait). Similarly to this behavioral evidence of reduced control in motor dis-engagement in PD patients, the electrophysiological investigation of beta oscillations also show a marked difference exactly in the release phase of the cyclic movement, where the second beta ERD is not seen during the shaking task (Fig. 3). In this light, our findings could also be interpreted as an electrophysiological correlate of impaired movement termination: During Shake, no beta ERD was measured when grip and load force decreased during the upward movement. Therefore, the missing beta desynchronization in the late phase of the cycling movement could be interpreted as a correlate for the reduced ability for movement termination in PD patients.

Similarly, the interplay between motor cortex and basal ganglia (as measured by PLV) was significantly reduced during Shake as compared to Press. When the functional connectivity to the motor cortex is high (as in Press) the temporal cueing in the basal ganglia seems to be more precise and more adaptive, as compared to Shake, where cortico-STN correlation is lower and therefore the temporal change in beta desynchronization during an ongoing movement is less adaptable.

5. Conclusions

The time-locked suppression of beta oscillatory activity in the STN is in line with previous reports of beta ERD prior to voluntary movements. Our results show that the STN is involved in anticipatory grip force control in PD patients. The difference in the phasic beta ERD between the two tasks and the reduction of cortico-subthalamic synchronization suggests that qualitatively different neuronal network states are involved in different grip force control tasks.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Neurobiology of Disease

Electrophysiological Evidence for Alternative Motor Networks in REM Sleep Behavior Disorder

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Patients with Parkinson's disease (PD) and REM sleep behavior disorder (RBD) show mostly unimpaired motor behavior during REM sleep, which contrasts strongly to coexistent nocturnal bradykinesia. The reason for this sudden amelioration of motor control in REM sleep is unknown, however. We set out to determine whether movements during REM sleep are processed by different motor networks than movements in the waking state. We recorded local field potentials in the subthalamic nucleus (STN) and scalp EEG (modified 10/20 montage) during sleep in humans with PD and RBD. Time-locked event-related β band oscillations were calculated during movements in REM sleep compared with movements in the waking state and during NREM sleep. Spectral analysis of STN local field potentials revealed elevated β power during REM sleep compared with NREM sleep and β power in REM sleep reached levels similar as in the waking state. Event-related analysis showed time-locked β desynchronization during WAKE movements. In contrast, we found significantly elevated β activity before and during movements in REM sleep and NREM sleep. Corticosubthalamic coherence was reduced during REM and NREM movements. We conclude that sleep-related movements are not processed by the same corticobasal ganglia network as movements in the waking state. Therefore, the well-known seemingly normal motor performance during RBD in PD patients might be generated by activating alternative motor networks for movement initiation. These findings support the hypothesis that pathological movement-inhibiting basal ganglia networks in PD patients are bypassed during sleep.

Key words: **β oscillations; Parkinson's disease; REM sleep behavior disorder; sleep; subthalamic nucleus**

Significance Statement

This study provides evidence that nocturnal movements during REM sleep in Parkinson's disease (PD) patients are not processed by the same corticobasal ganglia network as movements in the waking state. This implicates the existence of an alternative motor network that does not depend directly on the availability of L-Dopa in the basal ganglia. These findings further indicate that some PD patients are able to perform movements in the dopamine depleted state, possibly by bypassing the pathological basal ganglia network. The existence and direct activation of such alternative motor networks might finally have potential therapeutic effects for PD patients.

Introduction

Slowness of movement (bradykinesia) is the fundamental and most characteristic deficit in patients with Parkinson's disease (PD) (Marsden, 1989). Motor impairment in PD is linked to a complex dysfunction of the basal ganglia network, predominantly caused by progressive loss of nigrostriatal neurons (Obeso et al., 2000; Del Tredici et al., 2002). The subthalamic nucleus (STN) has been identified as a key structure for movement control, and many studies have linked hypersynchronous neuronal activity in the low β band (12–20 Hz) of subthalamic neurons with motor impairment (Brown et al., 2001; Quiroga-Varela et al., 2013). Within this framework, STN deep brain stimulation (DBS) is thought to counteract the pathologically elevated β activity, leading to significant motor improvement (Kumar et al., 2002; Kühn et al., 2008; Benabid et al., 2009). However, in addition to dopaminergic or neuromodulative interventions, also the external context of motor initiation modulates motor control. For example, PD patients with freezing of gait are typically able to switch from severe immobility to almost normal gait by use of external cues (Thaut et al., 1996; Burleigh-Jacobs et al., 1997; Nieuwboer et al., 2007). Similarly, strong emotions might lead to complete restoration of motor control, the extreme example being the anecdotal report of a PD patient with severe bradykinesia, who was able to escape rapidly from a house in a fire (Souques,

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The authors declare no competing financial interests.
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1921). Similarly, some PD patients show unimpaired motor control during REM sleep, a phenomenon known as REM sleep behavior disorder (RBD). These patients often perform surprisingly fast movements that are usually in relation to dream content (enacted dreams) (Schenck et al., 1986; De Cock et al., 2007). RBD episodes typically show strong emotional or violent characteristics (Comella et al., 1998); but also nonviolent behaviors, such as laughing or singing, have been reported (Oudiette et al., 2009; Siclari et al., 2011). Intriguingly, the seemingly unimpaired motor control in RBD patients stands in strong contrast to severe nocturnal bradykinesia due to reduced dopaminergic treatment during the night (De Cock et al., 2007).

However, little is known about the source of increased locomotor drive during REM sleep in RBD patients. Based on the observation that RBD movements include complex learned behavior, show predominance to the upper limbs (with larger cortical representations), and consist typically of sudden jerky ("unfiltered") movements, De Cock et al. (2007) proposed that basal ganglia networks are bypassed during REM sleep. This hypothesis was further supported by the finding that parkinsonism also disappeared during REM sleep in patients with multiple system atrophy who were not sensitive to L-Dopa (De Cock et al., 2011). In this line, a recent ictal-SPECT study revealed activation of premotor areas, but no involvement of the basal ganglia during RBD (Mayer et al., 2015). Together, these findings strongly support the hypothesis of basal ganglia being bypassed during RBD (Arnulf, 2012).

Electrophysiological studies in rodents (Urbain et al., 2000) and PD patients (Urrestarazu et al., 2009) revealed increased firing rate in the STN during REM sleep movements, in contrast to the otherwise observed decreased activity of STN neurons in self-initiated waking movements (Cassidy et al., 2002; Priori et al., 2002; Kühn et al., 2004). Furthermore, these studies suggested a fluctuating pattern of neuronal activity in the STN during REM sleep. However, the temporal evolution of β oscillations with respect to REM sleep movements is unknown.

In this study, we set out to determine whether different motor networks are active during movements in RBD compared with motor control in the waking state and during NREM sleep. To test this hypothesis, we recorded local field potentials (LFPs) in the STN in patients with RBD and analyzed event-related potentials upon movement initiation in REM sleep and in the waking state. Specifically, we asked whether the well-known time-locked modulatory effect of β oscillatory activity in the STN is also observed during REM sleep movements.

Materials and Methods

Patient selection and surgery. In the time period between January 1, 2013 and June 30, 2013, 13 PD patients were scheduled for implantation of deep brain electrodes in the STN in our clinic. Among those patients, we identified four patients (1 female and 3 males) with clinically manifest RBD. Based on clinical indication, bilateral DBS electrodes (model 3389, Medtronic) were implanted after MR-based direct targeting of the STN. Optimal electrode position was verified by microelectrode recordings, intraoperative test stimulation, and postoperative CT scan. For later analysis of LFPs in the STN, DBS wires were temporarily externalized before implantation of the impulse generator. The study protocol was approved by the local ethics review board (Kantonale Ethikkommission Zurich, KEK-ZH 2012–0327). All patients gave written informed consent for study participation.

Sleep recording and spectral analysis. Sleep analysis was performed in the second postoperative night (12 h recording: 8 P.M. to 8 A.M.), control tasks during the day before sleep recordings. All analyses were performed in L-Dopa OFF and stimulation OFF condition. We recorded scalp EEG from a 12-channel subset of the 10–20 system (Fp1/Fp2, F3/F4, C3/C4, O1/O2, Fpz/Fz/Cz/Oz), 2-channel electro-oculography (EOG), chin surface electromyography (EMG), and digital infrared video-monitoring. Simultaneously, we acquired bilateral LFPs from the STN (Xltek Mobee 32 EEG Unit, Natus Medical). The sampling rate for EEG, EOG, EMG, and LFP was 200 Hz.

Sleep stage scoring was performed visually on 30 s epochs according to revised standard criteria (Kales and Rechtschaffen, 1968; Iber et al., 2007). Scoring of REM sleep was based primarily on REM sleep-specific EEG and EOG patterns because REM-sleep atonia can be absent in patients with RBD.

For postprocessing of the subthalamic LFP, the raw signal was first rereferenced to a bipolar montage between subsequent electrode contacts on both sides (0–1; 1–2; 2–3, with 0 being the lowest and 3 the most cranial electrode contact). According to postoperative reconstruction of the electrode placement, contact 1 or contact 2 was found to be located in the dorsolateral STN in all patients. Therefore, all further analysis was pursued using the inner bipolar derivation (contacts 1 − contact 2) on both sides. For spectral analysis of the LFP signal, each 30 s epoch was subdivided in epochs of 5 s length. Artifacts were rejected by a semiautomated algorithm based on spectral power in the γ band (35–50 Hz). Then, we applied a fast Fourier spectral analysis on artifact-free 5 s epochs after multiplication with a Hanning window to address edge discontinuities (e.g., Brockwell and Davis, 2013). Finally, we collapsed and averaged all data according to sleep behavioral state. For comparison between individuals, all spectra were normalized to the total power (1–100 Hz).

REM sleep movements and control tasks. Two experienced sleep specialists (M.H. and E.W.) reviewed all nocturnal video-EEG recordings. Movements in REM sleep were defined as visually observable movements with simultaneously elevated EMG signal. Based on movement onset, we identified 20 s fragments of EEG and LFP (10 s before and 10 s after movement onset) for further analysis of event-related potentials.

As control tasks, all patients performed several self-initiated movements during wakefulness (repetitive self-paced shaking and pressing movements) measured by an inertial measurement unit as described previously (Imbach et al., 2015). As a second control experiment, we identified movements during NREM sleep. For both control conditions, we collected data fragments 10 s prior and 10 s after movement in the same way as for the REM sleep movements. Fragments with obvious movement artifacts were excluded after visual inspection of the raw data.

Analysis of event-related potentials. All selected data fragments were first bandpass filtered in a wide β range (13–35 Hz). Next, we calculated the Stockwell transform of each data fragment to obtain a high-resolution, time-frequency decomposition of the raw signal and averaged the time-frequency spectra among all movements (Stockwell et al., 1996). The temporal variation of β power before and after movement onset was then estimated by summarizing the total power in the β band (13–35 Hz) at each time point. Finally, we determined temporal synchronicity between the STN-LFP and the ipsilateral central EEG signal (C3/C4 electrode) by means of the phase locking value (Cohen, 2014). This approach was chosen for an accurate time-dependent analysis of synchronicity before and after movement onset. For this analysis, the instantaneous phase was estimated by first calculating the Hilbert transform of the raw signal. The phase locking value was then determined for each time point by summarizing phase differences in the complex plane between STN LFP and the ipsilateral central EEG signal over all trials (Cohen, 2014).

Statistical analysis. Data postprocessing, spectral analyses, and calculation of phase locking value were performed with customized scripts written in MATLAB (The MathWorks; www.mathworks.com, RRID: SCR_001622). We calculated two-sided Student's t tests and one-way ANOVA for comparison of two or multiple groups as applicable. Statistical significance was established at $p < 0.05$.

Results

Sleep-related movements

In total, we identified 113 artifact-free REM sleep movements, 30 standardized self-paced movements during WAKE, and 99 NREM sleep movements for further analyses. REM sleep move-

Table 1. Demographic data at the time of sleep EEG

ID	Gender	Age (yr)	PD subtype	Predominance[a]	Disease duration (yr)	LED (mg)	Time in REM (min)	No. of REM sleep movements	Predominant motor phenomena
1	Female	60	Rigid akinetic	Left	9	850	113	44	Movement of left arm; jerks of whole body
2	Male	63	Tremor	Right	12	1297	24	21	Jerks and movements of both legs
3	Male	68	Rigid akinetic	Right	11	1400	81	42	Jerks of head, whole body, and right arm; vocalizations
4	Male	72	Tremor	Left	11	760	44	6	Jerks of whole body

LED, Levodopa equivalent dose.

[a]PD symptom side predominance.

ments occurred primarily in the second half of the night. The observed predominant movement types during REM sleep were short-lasting unilateral and bilateral sudden jerks of the extremities (arms more than legs) and vocalizations. PD subtype (akinetic-rigid vs tremor dominant) had no influence on frequency and type of RBD movements. However, motor laterality of PD symptoms was linked to the predominant side of RBD movements, with more RBD movements on the predominant PD side. Patients' clinical characteristics and RBD movement types are summarized in Table 1.

Increased β oscillatory activity during WAKE and REM sleep

Power spectral density of the subthalamic LFP signal differed between sleep behavioral states. The most prominent difference was observed in the wide β range (13–35 Hz). We found a significant increase of relative power spectral density in the β range during WAKE and REM sleep compared with slow-wave sleep. Total LFP β power did not differ significantly between WAKE and REM. In the α and θ range, we found no significant differences of spectral density between sleep behavioral states (Fig. 1).

Paradoxical β synchronization in REM sleep movements

Considering the selectively elevated power spectral density in the β range during REM sleep and WAKE (Fig. 1), all signals were β bandpass filtered (13–35 Hz) for further analysis of event-related potentials. In agreement with previous studies, we found a significant β desynchronization in the STN during movements in the off-medication waking state (Fig. 2*A*). β power was significantly different from baseline condition 2.5 s after movement onset (Fig. 2*B*). In contrast, during movements in REM sleep, we observed marked β synchronization with onset before the observed movement initiation. β synchronization reached a significant level 3.3 s before visually observable movements (Fig. 2*C*,*D*). During NREM sleep movements, we observed a similar pattern of time-locked β synchronization with significant increase 2.7 s before movement onset (Fig. 2*E*,*F*). Pairwise comparison of β power before and after movement onset revealed a significant decrease in β power during WAKE movements ($p < 0.05$) and even more pronounced increase during REM and NREM sleep movements ($p < 0.005$; Fig. 2*B*,*D*,*F*).

Reduced corticosubthalamic synchronicity during REM sleep movements

Comparing the phase locking value between the STN and the ipsilateral motor cortex in the perimovement period 5 s before and after movement initiation, we found no relevant modulation of phase locking for WAKE movements (Fig. 3*A*). In contrast, during REM sleep, corticosubthalamic synchronicity (as measured by phase locking) in the β range was reduced after movement onset, indicating a decoupling of the basal ganglia from cortical neurons. Similarly, pairwise comparison of phase locking before and after movement initiation for all individuals showed

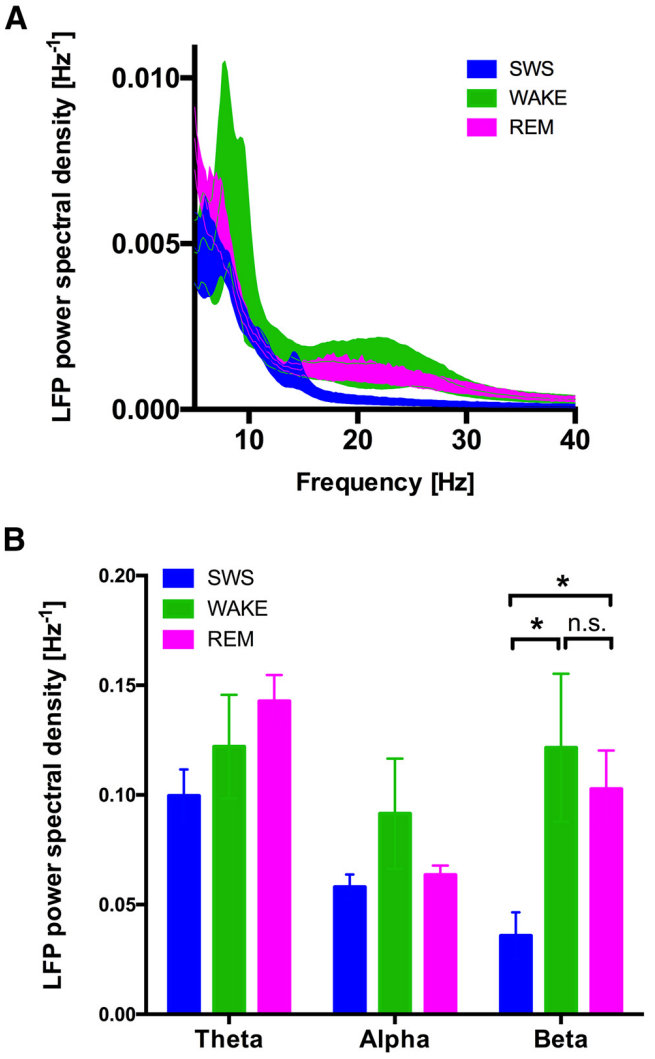

Figure 1. Power spectral density of subthalamic neurons according to behavioral state. ***A***, Power spectral density of LFPs in the STN are shown in a 40 Hz spectrogram. REM sleep (magenta) and WAKE (green) show elevated β power compared with NREM sleep (blue). Ribbon represents SEM. ***B***, Cumulative power in different frequency bands shows selective increase of β power during REM sleep and WAKE. No differences are observed in the α and θ range. Frequency bands: θ, 4–8 Hz; α, 8–13 Hz; β, 13–35 Hz. *$p < 0.05$.

significantly decreased synchronicity in the β range during ongoing movements in REM sleep compared with the average phase locking value before the movement. Again, for WAKE movements, we found no significant differences comparing the phase locking value before and after movement initiation (Fig. 3*B*). Phase locking analysis of NREM sleep movements revealed a higher baseline level of synchronicity during NREM sleep compared with REM sleep and WAKE. During NREM sleep movements, we found reduced corticosubthalamic synchronicity after movement onset, as observed during REM sleep movements (Fig. 3).

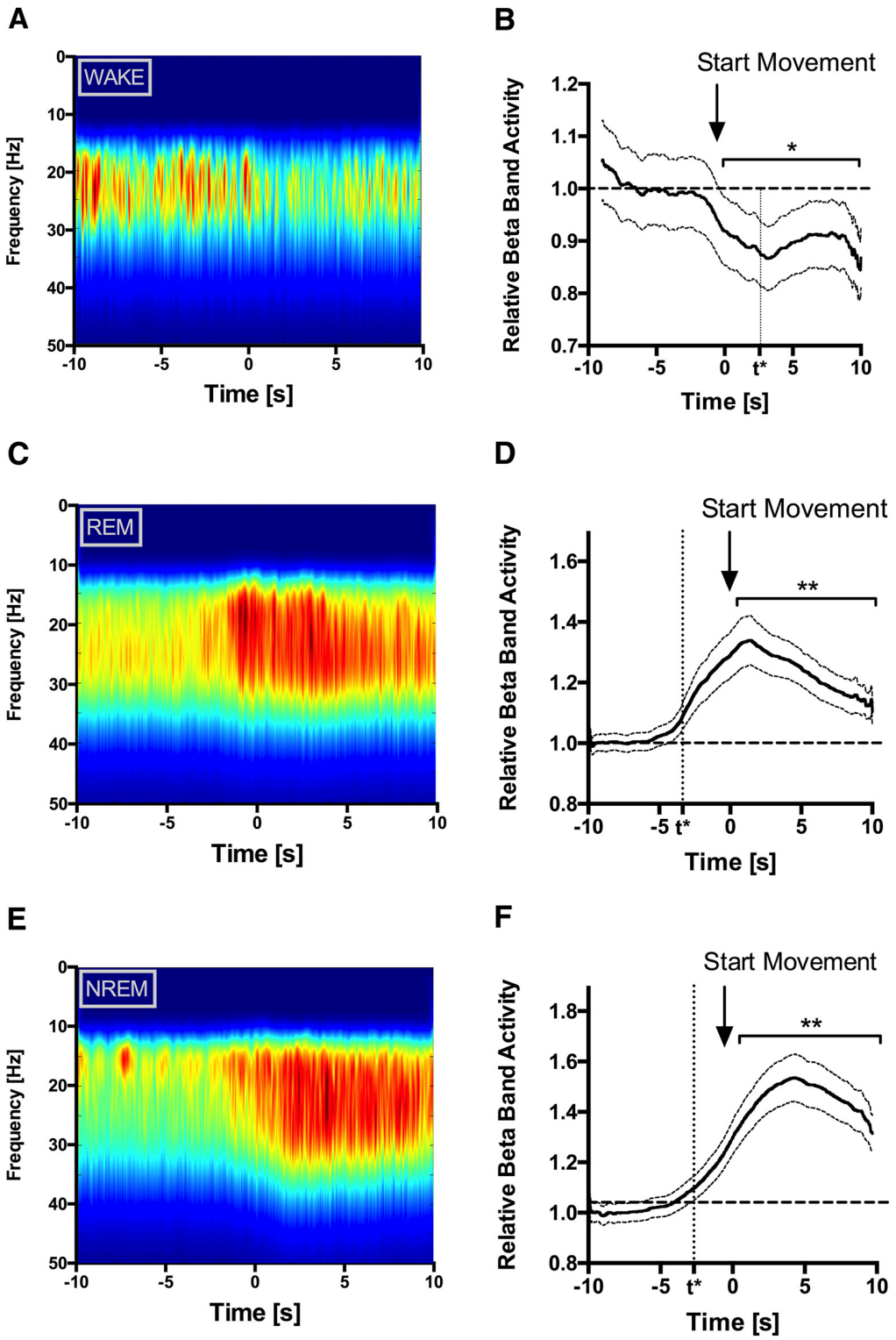

Figure 2. β modulation in the STN during WAKE and REM sleep movements. Time-frequency spectra of β filtered STN LFP in the period 5 s before and after movement initiation show β desynchronization during WAKE movements (***A***, WAKE) and increased β activity during REM sleep movements (***C***, REM) and NREM sleep movements (***E***, NREM). Time-frequency spectra show averaged S-transform values over all patients and all movements: WAKE, $n = 30$; REM, $n = 113$; NREM, $n = 99$. Right panels, Mean β activity as normalized to the 5 s period before movement initiation for WAKE (***B***), REM sleep (***D***), and NREM sleep (***F***). Pairwise comparison of β power before and after movement onset showed significant decrease during WAKE and increase during REM and NREM (horizontal line). ***B***, ***D***, ***F***, $^*p < 0.05$; $^{**}p < 0.005$. Time points for the first significant difference (defined as a difference $>2 \times$ SD) of β power compared with baseline are shown as additional time points on the *x*-axis (t*).

Discussion

Parkinson patients with RBD show relatively unimpaired motor function during REM sleep. However, the mechanism allowing for this temporary normalization of motor control is unknown. Considering the overwhelming data on impaired basal ganglia function in PD patients in the L-Dopa off state, the question arises how rapid motor output is possible despite the motor-inhibiting network state of basal ganglia during sleep. At least two explana-

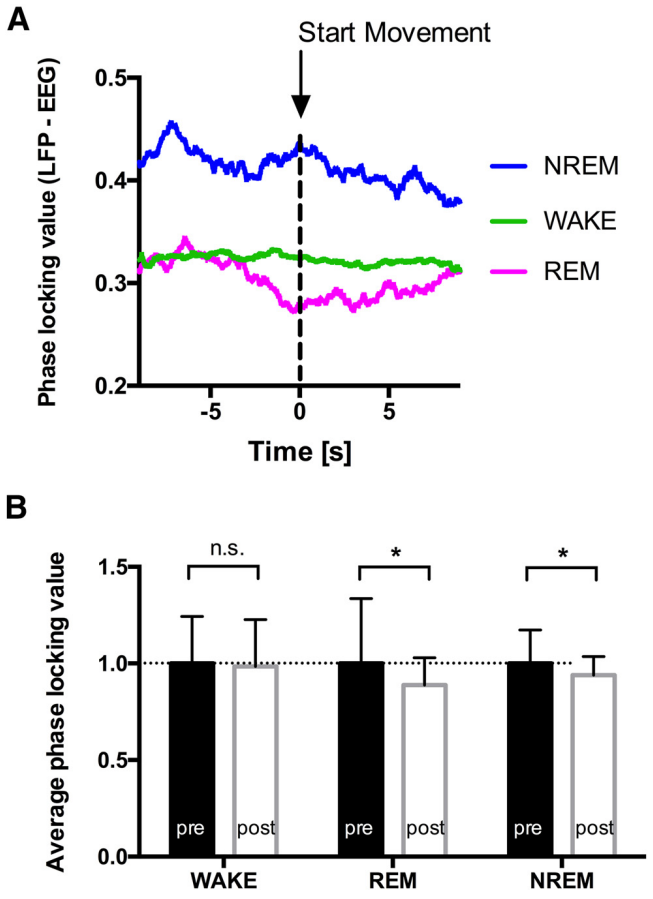

Figure 3. Synchronicity between STN and motor cortex during WAKE and REM sleep movements. ***A***, The temporal evolution of the phase locking value is shown for the period 5 s before and after movement onset. During REM sleep movements, a reduced synchronicity was observed, whereas no modulation of the phase locking was found during WAKE. NREM sleep showed a higher baseline synchronicity with reduction upon movement initiation. ***B***, Pairwise comparison of normalized phase locking values of the period prior (pre) and after (post) movement onset showed a significant difference only during REM and NREM sleep movements: WAKE, $n = 30$; REM, $n = 113$; NREM, $n = 99$. $^*p < 0.05$.

tions can be discussed for this phenomenon: First, REM sleep could have a direct influence on pathological basal ganglia networking in an analogous way as L-Dopa administration or chronic electrical stimulation of the STN. In this view, the modified global brain state during REM sleep would normalize basal ganglia function, mimicking an instantaneous dopaminergic disinhibition of the basal ganglia, eventually leading to unimpaired motor output. Alternatively, the pathological inhibitory corticobasal ganglia network could be bypassed during REM sleep, as suggested by others previously (De Cock et al., 2011; Arnulf, 2012). In this model, REM sleep movements are not processed by dopamine-depleted basal ganglia, but by an alternative (yet unknown) central motor control network without direct interaction with the basal ganglia. In other words, we set out to determine whether the basal ganglia networks are modulated or merely bypassed during RBD.

Considering the outstanding role and well-described modulatory effects of β oscillations in the STN, the measurement of STN LFPs during REM sleep movements provides a direct possibility to test these hypotheses: β oscillations of subthalamic neurons are known to be desychronized during WAKE movements, imaginary movements, L-Dopa administration, or chronic DBS (Priori et al., 2002; Kühn et al., 2004, 2006; López-Azcárate et al., 2010). Now, if REM sleep movements are also processed by the basal ganglia, one could expect a similar β desynchronization before and during movements in REM sleep. Thus, our problem simplifies to the question: Are β oscillations desychronized during paradoxical REM sleep movements or do we observe a different network activity in the basal ganglia during REM sleep?

This study provides compelling further evidence that REM sleep movements are processed by an alternative network showing different patterns of β modulation compared with WAKE movements. In contrast to the well-known β desynchronization during WAKE movements, we found β power to be significantly enhanced during REM sleep movements. In a simplified model for basal ganglia function in the waking state, β oscillations in the STN can be interpreted as an alternating go/no-go signaling (with β desynchronization corresponding to "go" and β synchronization signifying "no-go"). In this analogy, our findings suggest that the functional state of the basal ganglia translates to a motor inhibitory signal (no-go), exactly during ongoing REM sleep movements. Therefore, the observed paradoxical β synchronization in the STN supports the previous hypothesis that pathological basal ganglia signaling might be bypassed during REM sleep (De Cock et al., 2007).

Our findings are in agreement with earlier human (Urrestarazu et al., 2009) and rodent (Urbain et al., 2000) studies showing intermittent increased β activity in relation to REM sleep movements. However, in addition to these previous studies, the observed event-related β synchronization upon movement initiation in REM sleep provides further evidence for a direct interplay between RBD movements and β synchronization in the STN.

The observed analogous temporal modulation of β activity in NREM and REM sleep may indicate a common alternative pathway for all sleep-related movements (NREM and REM). Therefore, the question arises whether the observed synchronization reflects physiologically altered motor activation during sleep in general. However, in this study, we only examined patients with definitive RBD; therefore, the observed synchronization in NREM sleep movements might still represent a specific effect of altered motor control in RBD patients. Nevertheless, further studies might address these issues (e.g., by performing analogous analyses in a comparative approach in PD patients with and without RBD).

As a limitation of our study, motor behavior during REM sleep was significantly different from waking movements (sudden jerky RBD movements vs smooth repetitive movements in WAKE), and this difference in motor output might directly influence β oscillatory activity in the STN. However, as many previous studies generally showed β desynchronization upon movement initiation in the waking state (Priori et al., 2002; Kühn et al., 2004; López-Azcárate et al., 2010), we consider our finding not to be fully explained by the different characteristic of motor output alone.

Corticobasal ganglia coherence is a measure to quantify the synchronicity of neuronal activity between the STN and the motor cortex. We found that, during REM sleep, cortico-STN coherence was significantly reduced compared with WAKE movements. Again, this finding supports the hypothesis that REM sleep movements are not processed by the "conventional" corticobasal ganglia pathway, but by other (possibly subcortical) networks.

We can only hypothesize upon the origin of the observed time-locked β synchronization during sleep-related movements. The hyperdirect pathway provides direct activating input from cortical areas (e.g., the presupplementary motor area) to the

STN, leading eventually to movement inhibition, and can be interpreted as an early inhibitory signal during movement preparation to provide appropriate movement selection through the later to start activating direct pathway (Aron, 2011; Jahanshahi et al., 2015). In this line, we speculate that, during sleep-related movement, the hyperdirect pathway might be activated before the movement to prevent early movement initiation (possibly in a similar way as in the waking state); but due to the proposed basal ganglia bypassing during sleep, this early STN synchronization is not followed by β desynchronization by means of the direct pathway. This model could also explain why β synchronization was observed before visible movement onset during sleep.

Finally, the reason for the hypothesized bypassing of the basal ganglia in PD patients with RBD remains unknown. Considering the strong association of RBD with PD, one might speculate that pathologically reduced modulating activity in the extrapyramidal system results in compensatory overactivity of the direct pyramidal or another pathway that can apparently be unlinked from the basal ganglia during sleep by means of a yet unknown mechanism.

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Functionally separated networks for self-paced and externally-cued motor execution in Parkinson's disease: Evidence from deep brain recordings in humans

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A B S T R A C T

Spatially segregated cortico-basal ganglia networks have been proposed for the control of goal-directed and habitual behavior. In Parkinson's disease, selective loss of dopaminergic neurons regulating sensorimotor (habitual) behavior might therefore predominantly cause deficits in habitual motor control, whereas control of goal-directed movement is relatively preserved. Following this hypothesis, we examined the electrophysiology of cortico-basal ganglia networks in Parkinson patients emulating habitual and goal-directed motor control during self-paced and externally-cued finger tapping, respectively, while simultaneously recording local field potentials in the subthalamic nucleus (STN) and surface EEG. Only externally-cued movements induced a pro-kinetic event-related beta-desynchronization, whereas beta-oscillations were continuously suppressed during self-paced movements. Connectivity analysis revealed higher synchronicity (phase-locking value) between the STN and central electrodes during self-paced and higher STN to frontal phase-locking during externally-cued movements. Our data provide direct electrophysiological support for the existence of functionally segregated cortico-basal ganglia networks controlling motor behavior in Parkinson patients, and corroborate the assumption of Parkinson patients being shifted from habitual towards goal-directed behavior.

Introduction

Patients with Parkinson's disease (PD) suffer from progressive impairment of motor control caused by a loss of dopaminergic neurons in the basal ganglia (Obeso et al., 2000). The resulting complex dysfunction of the basal ganglia motor network impairs motor function on a general level causing slowness of movement (also referred to as bradykinesia), among other symptoms. Despite the universal impairment of motor execution in PD, the context of motor initiation severely modulates motor performance: For instance, motor function can be drastically improved in PD patients by providing salient visual or auditive cues (Jahanshahi et al., 1992; Rogers et al., 1998; Hallett, 2008; Nonnekes et al., 2015). However, the reason for this striking dichotomy between spontaneous (internally-triggered) and cued (externally-triggered) movements is not fully understood.

We propose to contextualize this dichotomy in terms of habitual (i. e., spontaneous, sensorimotor, over-trained) versus goal-directed (i. e. novel, associative) motor control (Poldrack et al., 2005; Graybiel, 2008). Redgrave and co-workers (Redgrave et al., 2010) proposed that in the Parkinsonian state, control of habitual behavior is more severely impaired than goal-directed behavior, resulting in the progressive reliance on goal-directed motor control. Thus, PD patients are gradually forced to rely on their slower and computationally more intensive goal-directed motor control, even for the execution of over-trained habitual motor functions.

This intriguing hypothesis is fueled by the identification of spatially segregated functional neuroanatomical cortico-subcortical networks for the control of habitual and goal-directed behavior in humans (Nakano et al., 2000; Wiesendanger et al., 2004; Jahanshahi et al., 2015), non-human primates (Monakow et al., 1978; Carpenter et al., 1981; Romanelli et al., 2005; Chersi et al., 2013), and rodents (Gremel and Costa, 2013). Furthermore, mounting evidence from anatomical, neurophysiological and clinical studies corroborate the hypothesis of a tripartite organization of the human STN (Krack et al., 2001; Mallet et al.,

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2007; York et al., 2009; Accolla et al., 2016), although the segregation into sensorimotor, associative, and limbic territories also shows substantial areas of overlap (Haynes and Haber, 2013; Accolla et al., 2016). Associative and sensorimotor information is conveyed from respective areas within the cerebral cortex to the basal ganglia through segregated loops (Alexander et al., 1986) and relayed through the basal ganglia in a topographically organized fashion (Lehericy et al., 2004; Draganski et al., 2008), making the basal ganglia an integrative part in the processing of habitual and goal-directed behavior. Selective dopamine depletion in the basal ganglia regions controlling habitual behavior (habitual motor networks) might therefore cause predominant impairment of habitual motor control, leaving goal-directed motor performance relatively preserved (Redgrave et al., 2010; de Wit et al., 2011). Given the clinical observation that external cues facilitate voluntary movements in PD patients, we hypothesize that externally-cued movements are generated within goal-directed motor networks, whereas more severely affected, self-paced motor control is generated within the predominantly impaired habitual motor networks.

The question remains, however, whether the hypothesized behavioral segregation is also reflected on an electrophysiological level in humans. Furthermore, little is known about particular thalamocortical underpinnings of both behaviors such as steady-state power spectral densities, event-related synchronicity and phase-coupling within the proposed networks. In the basal ganglia, beta-oscillatory activity is assumed to play a predominant role in the control and modulation of motor activity, and beta-oscillations (13–35 Hz) in the subthalamic nucleus (STN) are correlated with the generation and persistence of the Parkinsonian state: Subthalamic beta-power is pathologically increased in PD patients (Brown et al., 2001; Hammond et al., 2007; Ray et al., 2008), a reduction of signal power in the beta-band correlates with clinical improvement (Kuhn et al., 2006a,b; Kuhn et al., 2008), and both the administration of levodopa (Brown et al., 2001; Lopez-Azcarate et al., 2010) and high-frequency DBS (Kuhn et al., 2008; Eusebio et al., 2011) lead to a suppression of beta-synchronicity. Moreover, stability in the beta-band has been correlated with the severity of motor impairment (Little et al., 2012; Tinkhauser et al., 2017), and the suppression of beta-activity prior to movement initiation in event-related tasks is necessary for motor control, thus further corroborating the putative anti-kinetic effect of beta-oscillations within the basal ganglia (Brown et al., 2001; Kuhn et al., 2006a, b; Androulidakis et al., 2008; Oswal et al., 2012), albeit shorter periods of beta-synchronization may represent physiological signaling in the context of normal motor control (Feingold et al., 2015; Tinkhauser et al., 2017). In this line, external behavioral cues lead to event-related beta-desynchronization in the basal ganglia (Williams et al., 2003; Kuhn et al., 2004). Nevertheless, more recently, increased beta-power after salient cues has also been reported in non-human primates (Leventhal et al., 2012).

In summary, the spatially segregated associative and sensorimotor cortico-basal ganglia circuits and the striking dichotomy in motor performance between habitual and goal-directed motor control strongly suggest that distinct neuronal networks are recruited for different motor behaviors in PD. If this hypothesis holds true, the proposed complementary networks should also have a direct electrophysiological correlate in subcortical as well as cortical areas. Considering the outstanding role of subthalamic beta-oscillations in movement control, we specifically investigated whether a shift from habitual to goal-directed control is reflected in a change of beta-activity on the basal ganglia level. We set out to test this hypothesis by measuring deep brain and surface neuronal activity in PD patients engaged in self-paced index finger tapping (habitual paradigm) and subsequent analogous externally-cued tapping (goal-directed paradigm) directed by acoustic cues. These experiments aim at filling the missing link between the structural (anatomical) and functional (behavioral) model of the cortico-subcortical interplay in movement control on an electrophysiological level.

Materials and methods

Patients and surgery

Between March 2016 and January 2017, we included nine PD patients (Table 1) undergoing bilateral DBS lead implantation into the STN (Model 3389, Medtronic Neurological Division, Minneapolis, MN, USA). We did not include patients that were unable to be in L-Dopa OFF, had severe dyskinesia, or refused to participate. DBS leads were implanted after MRI-based direct targeting of the STN. Accurate implantation of the leads within the STN was intraoperatively verified by micro-electrode recordings (Leadpoint, Medtronic, Minneapolis, MN, USA) in steps of 0.5 mm until target, starting 10 mm above the target, clinical response upon intraoperative stimulation, and intraoperative computed tomography. We verified accurate electrode position by comparison of planned and actual post-operative electrode position in the computed tomography. All experiments were performed on the second postoperative day in L-Dopa OFF and DBS OFF state, prior to connecting the leads to the subcutaneously implanted stimulation device 3–5 days after lead implantation. Decisions on patient selection and surgical procedures were not affected by this study and exclusively based on clinical grounds. This study was approved by the local ethics committee (Kantonale Ethikkommission Zürich, board decision on the amendment to KEK-ZH: 2012–0327), and all patients gave informed written consent prior to study participation.

Experimental setup and motor tasks

We measured EEG signals from scalp electrodes and STN local field potentials (LFPs) from temporarily externalized DBS wires (4 electrode sites per lead) sampled at 200 Hz by a Mobee 32 EEG recorder (Xltek, Natus, Medical Incorporated, Pleasanton, CA, USA). For the scalp EEG, we used a 12-channel subset of the 10–20 system at the frontopolar (Fp_1/

Table 1
Demographics and clinical patient characteristics. MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; ON/OFF values of preoperative L-Dopa challenge test; LED: preoperative levodopa equivalent dose (Tomlinson et al., 2010). The third part of the MDS-UPDRS includes the clinician-scored, monitored motor evaluation (33 scores based on 18 items) (Goetz et al., 2008), ranging from the worst MDS-UPDRS III score of 132 (= 4 · 33) points to 0 points, with all items scoring the same as in healthy individuals. The minimal clinically important difference on the UPDRS motor score is 2.3–2.7 points (Shulman et al., 2010).

ID	Age [y]	Gender	Parkinson type	Side dominance	Disease duration [y]	Hoehn-Yahr Scale	MDS-UPDRS III ON/OFF	LED [$\frac{mg}{d}$]
1	56	M	Equivalent	L	8	2.0	11/28	475
2	55	M	Akinetic-rigid	R	5	2.0	12/17	1′300
3	58	F	Akinetic-rigid	L	11	3.0	9/32	1′319
4	48	M	Equivalent	L	5	1.5	6/19	1′150
5	62	M	Equivalent	R	6	2.5	14/41	800
6	64	F	Tremor	L	9	2.0	12/20	480
7	73	F	Equivalent	R	15	4.0	37/69	1′600
8	51	F	Akinetic-rigid	L	10	2.0	20/29	1′030
9	54	M	Akinetic-rigid	R	5	2.0	11/32	1′331

Fp_2), frontal (F_3/F_4), central (C_3/C_4), occipital (O_1/O_2) and midline (C_z/P_z) electrode sites. We placed the recording reference and the ground near C_z. Electrode impedances were set <5 kΩ. Electrodes C_3 and C_4 were slightly shifted laterally (<2 cm) if in conflict with the exit point of the DBS wires through the burr holes. Signal quality was checked visually for electrode or movement artifacts. A representative 10 s epoch of LFP, EEG and tapping force data is shown in the appendix (Supplementary Fig. 1).

All motor experiments were performed in a sitting position with eyes closed and separately for both hands, starting with the more severely affected side. First, we recorded a resting state condition as baseline during 90 s for each patient (eyes closed, no movement). Thereafter, we instructed patients to perform self-paced arrhythmic index finger tapping for a period of 90 s within a constructed frame of a given amplitude (Fig. 1A). Patients were instructed to alternately touch the upper and lower force sensor at a random interval of approximately 1–2 s without further constraints (resulting in 45–90

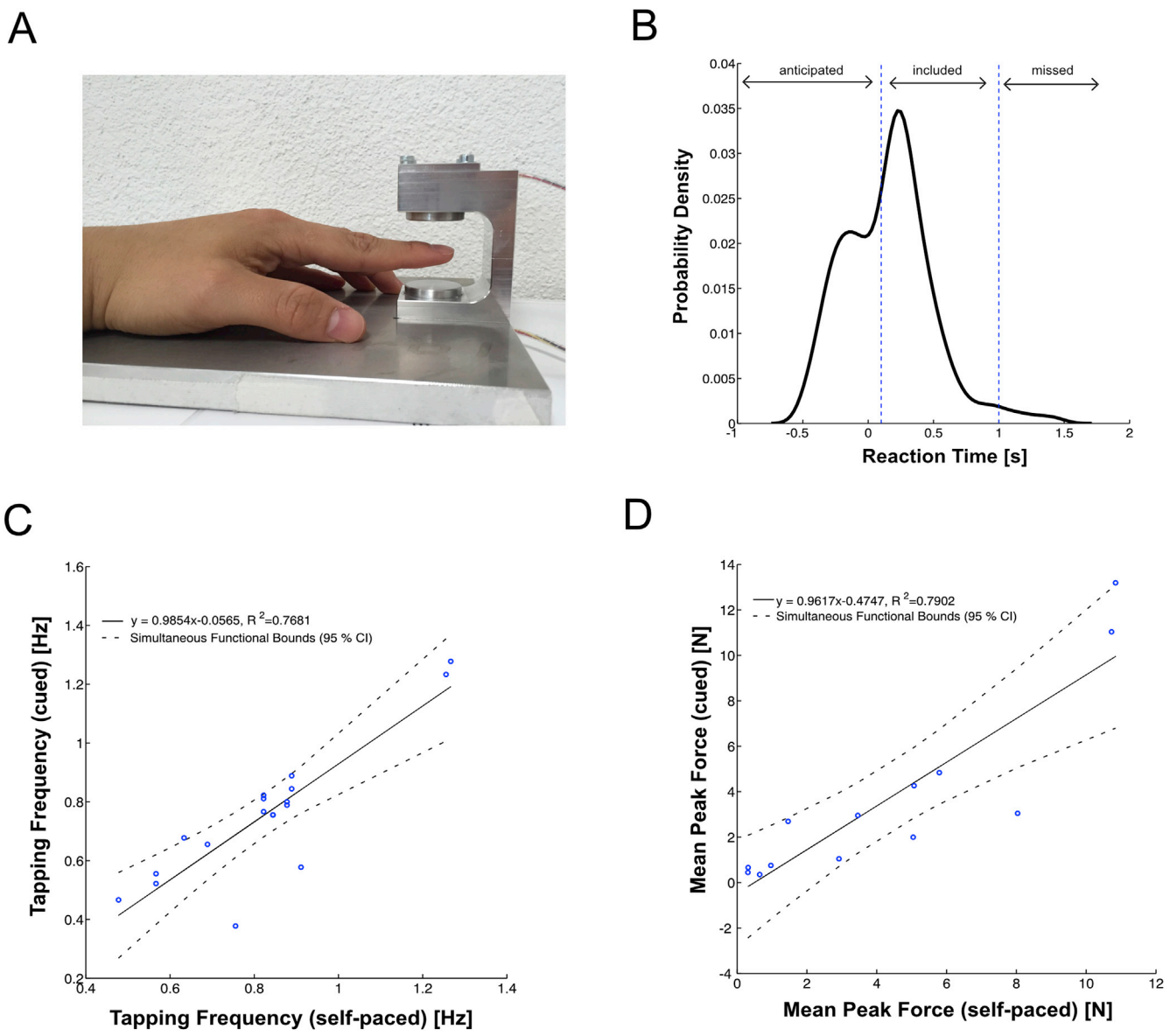

Fig. 1. a) Experimental setup. Patients moved their index finger in an up-and-down fashion, thereby touching the two force sensors located above and below the finger. This movement was either self-paced or externally-cued.

b) Distribution estimate of reaction times. The distribution estimate of the reaction times ($n = 809$) during the externally-cued tapping experiments ($N = 13$), with the mode at 0.23 s, followed a bimodal pattern that was highly suggestive for two types of tapping, namely anticipated and truly cued tapping. We included an average of 55% of taps per externally-cued experiment for further analyses after exclusion of taps occurring earlier than 0.1 s after the cue, thereby eliminating anticipated taps, or more than 1 s after the cue (vertical dashed blue lines).

c) Correlation of tapping frequencies between the self-paced and their subsequent externally-cued experiments. Recorded tapping frequencies (blue circles) were highly correlated ($R^2 = 0.7681$, $p < 0.001$, $n = 13$) between the initial self-paced tapping experiments and their respective subsequent externally-cued experiments, in which tapping was cued by the rhythm recorded during the preceding self-paced tapping. The calculated linear model $y = 0.9854\,x - 0.0565$ (black line; dotted black lines: 95% confidence interval of the simultaneous functional bounds) is almost identical to the linear equation $y = x$, stating that the tapping frequencies during the two paradigms are identical.

d) Correlation of mean peak forces during self-paced tapping experiments and their subsequent externally-cued tapping experiments. Recorded mean tapping peak-forces were highly correlated ($R^2 = 0.7902$, $p < 0.001$, $n = 13$) between the initial self-paced tapping experiments and their respective subsequent externally-cued experiments. The calculated linear model $y = 0.9617\,x - 0.4747$ (black line; dotted black lines: 95% confidence interval of the simultaneous functional bounds) is almost identical to the linear equation $y = x$, stating that mean peak-forces during the two paradigms are identical.

taps during the 90 s experiments). Tapping forces were measured using two force sensors (Cento Newton 10 N force transducers, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland) (Fig. 1A) and recorded by a NI–6009 data acquisition card (National Instruments Corporation, Austin, Texas, USA), sampled at 1 kHz. Post-recording time-synchronization between the EEG and the force recorder was enabled by a custom-programmed Arduino Uno micro-controller board (Arduino LCC) simultaneously emitting characteristic pulses to both recording devices. We implemented a custom-written peak-extraction algorithm to determine the peak-force time for every finger tap during the self-paced experiment. These peak-force times were used to generate the acoustic stimulus pattern for the subsequent 90 s externally-cued experiment, assigning a lower pitch tone to peaks recorded at the lower force sensor and a higher pitch tone to peaks recorded at the upper force sensor. Patients were then instructed to touch the upper or lower sensor following the higher or lower cueing sound, respectively. The experimental setup was designed such as to produce identical motor output (in terms of frequency, amplitude and peak grip force) between both paradigms, as the cues for the externally-cued task were directly derived from the previous self-paced finger tapping of the same patient. It also served to assess motor performance of the participants. We used the raw data from the force sensors to locate individual tap onsets (force derivative, $\dot{F}$, above 10% of maximum, as in (Blefari et al., 2015)) and calculated reaction times for the externally-cued task as the time difference between cue and tap onset (Fig. 1B). To test for agreement in motor performance between the externally-cued and self-paced experiments, mean tapping frequencies (Fig. 1C) and mean peak forces (Fig. 1D) were correlated, indicating good protocol adherence and comparable motor output. In other words, all patients performed simple self-paced and externally-cued motor tasks using different paradigms, but producing very similar motor output. To optimize the quality of behavioral assessments, we defined rigorous standards for included trials: movements with short reaction times (<100 ms, anticipated) or very late movements (>1000 ms, missed) were excluded from further analyses (Fig. 1B). Through this strong selection process, we were able to exclude inappropriate movements (anticipated or missed) and ensured that only truly cued finger taps were included for further data analysis of externally-cued movements.

Steady-state spectral analysis during rest and movement

To measure the spectral properties of the LFP signal in the contralateral STN during the states of rest, self-paced and externally-cued tapping movement, we calculated the average power spectral density (PSD) during the 90 s experiments using a modified periodogram approach (Welch, 1967) (256 samples Hanning window, 50% window overlap, 200 Hz sampling rate). As each DBS lead entails four contact sites, three bipolar recordings were possible for the analysis of the STN signal. For every patient, we first identified the bipolar recording site that showed the highest cumulative beta-power during rest, and used this derivation for all further analyses (middle position: 62.5%, upper and lower position: 18.75% each). To compare the average spectral power during both behavioral paradigms with the rest condition, the PSDs were first averaged over the lower (13–20 Hz), the higher (20–35 Hz), and a patient specific band (beta-peak frequency ± 5 Hz). These and all further non-statistical analyses were implemented in custom-written MATLAB scripts (R2016a, The MathWorks, Inc., Natick, Massachusetts, USA). We then used R (version 3.1.1) (R Core Team, 2014) and *lme4* (Bates et al., 2015) to perform linear mixed effects analyses of the relationship between behavior (rest vs. self-paced or externally-cued tapping) and the steady state spectrum in the low, high and the patient-specific beta-band. For this and all other linear mixed effects analyses in this study, we entered subject as a random effect and calculated *p*-values by likelihood ratio tests. Here, we tested the full model with the fixed effect of behavior against the model without the fixed effect of behavior.

Event-related beta-power analysis

Here, we set out to compare event-related beta-power modulation in the STN during self-paced and externally-cued tapping. We used tap onsets as events for the analysis of event-related beta-power modulation and event-related phase-synchronization in the STN-specific beta-band (beta-peak frequency ± 5 Hz). For the event-related beta-power analysis, we first calculated time-frequency representations of the STN-specific band around each event using Stockwell transforms (as in (Hackius et al., 2016)). Each time-frequency representation underwent voice-normalization (i.e. normalization of the time-dependent power along each frequency by their average between −1 and −0.5 s). All normalized event time-frequency representations from one experiment were point-by-point averaged and subsequently summarized across the frequency-domain, thereby yielding a STN-specific band power modulation around tap onset. As significant desynchronizations mainly occurred between 0 and 0.6 s, we calculated a cumulative STN-specific band power between 0 and 0.6 s for direct comparison of the self-paced and the corresponding externally-cued experiments. A linear mixed effects analysis was then performed to investigate the fixed effect of behavior (self-paced vs. externally-cued tapping) while entering subject as a random effect.

Analysis of event-related phase-synchronization

For cortico-subthalamic connectivity analysis (Litvak et al., 2012; van Wijk et al., 2017), we calculated the phase locking value (PLV) (Lachaux et al., 1999) to investigate synchronicity of neuronal oscillations between surface EEG and subthalamic LFP during self-paced as compared to externally-cued movement. A custom-written MATLAB-script filtered the EEG- or subthalamic LFP-signal in the patient-specific beta-band (beta-peak frequency ± 5 Hz, order of the finite impulse response filter = 40 data points) and calculated the locking of instantaneous phases obtained after Hilbert transformation according to the PLV formula (Lachaux et al., 1999). Unlike coherence, PLV is not confounded by amplitude correlation and is therefore more reliable for the direct comparison of motor paradigms that elicit a markedly different power-modulation in the frequency of interest. Using all four electrode contacts in both DBS leads, piercing the tripartite STN (sensorimotor: dorsolateral STN, associative: ventromedial STN) and the corresponding surface EEG electrodes over its projections (sensorimotor: primary motor cortex and supplementary motor area (SMA); associative: premotor cortex, prefrontal cortex, pre-SMA, SMA, frontal eye field) (Nambu et al., 1996; Tewari et al., 2016), we defined an *associative* loop, L_A (lowermost bipolar DBS lead derivation and frontal EEG electrodes), and a *sensorimotor* loop, L_{SM} (uppermost bipolar DBS lead derivation and central electrodes) (Fig. 4A and B). L_{SM}-phase-synchronicity was calculated as the PLV between central cortical electrodes (C_3/C_4) and the dorsolateral (sensorimotor) part of the STN (uppermost bipolar DBS electrode derivation) contralateral to the tapping finger, whereas L_A-phase-synchronicity was calculated as the PLV between frontal cortical electrodes (F_3/F_4) and the ventromedial (associative) part of the STN (lowermost DBS electrode derivation). Analogous to the event-related beta-power analysis, we determined instantaneous PLVs around tap onset (events, $t = 0$ s) after normalization of each fragment to the mean PLV between −1 and −0.5 s (prior to movement onset). Peri-movement changes in synchronization were compared between the two cortico-subthalamic loops and separately for the self-paced and the externally-cued experiments. All fragments of normalized instantaneous PLVs within the first cortico-subthalamic loop from one experiment were point-by-point averaged, and the mean of the PLV between 0 and 0.6 s was determined for later statistical comparison (linear mixed effects analysis, fixed effect of loop, random effect of subject) with the values obtained in the

second cortico-subthalamic loop during the same experiment.

Results

Behavioral motor output

After exclusion of movements that were anticipated (<0.1 s reaction time) or missed (>1 s reaction time), we retained on average 55% of all finger taps per experiment for further analyses (Fig. 1B). In total, we included 809 single movements for the self-paced experiments and 458 movements during the externally-cued motor paradigm. The average reaction time from cue to tap onset was 0.36 s. The median peak force over experiments was 5.25 N at the lower sensor during externally-cued tapping and 5.76 N during self-paced tapping. At the upper sensor, peak force was 2.18 N during externally-cued tapping and 2.24 N during self-paced tapping (no significant differences). Median tapping frequencies and peak force values between self-paced and cued tapping experiments were highly correlated ($R^2 = 0.7681$, $p < 0.001$ and $R^2 = 0.7902$, $p < 0.001$, respectively) with linear models close to $y = x$ ($y = 0.9854\ x - 0.0565$ and $y = 0.9617\ x - 0.4747$, respectively) (Fig. 1C and D), indicating that both movement paradigms produced almost identical motor output with respect to mean tapping frequency and mean peak force. One patient was excluded from the analysis due to non-adherence to the protocol, several episodes of falling asleep and multiple artifacts in the EEG signal during visual inspection (9–1 = 8 patients); additionally, three pairs of self-paced and externally-cued experiments (and thus the recordings from the contralateral STN) were excluded due to low signal quality or predominantly anticipated movements in one extremity resulting in a total number of 13 pairs of self-paced and externally-cued experiments.

Power spectral densities during rest and during self-paced and externally-cued movement

Spectral analysis during movement as compared to resting state revealed desynchronization in the high beta-band during both movement paradigms (Fig. 2A). Statistical analyses using a linear mixed effects model revealed that only self-paced tapping (as compared to rest) affected the steady-state power spectral density of the high-beta band ($\chi^2(1) = 4.20, p = 0.04031$), representing a significant desynchronization in the high-beta band during self-paced movements. In contrast, no significant changes were observed during externally-cued movements or in any of the other beta-bands during self-paced movements (Fig. 2B).

Event-related changes in beta-power

In contrast to the tonic desynchronization in the STN-specific beta-band during self-paced motor control, we found time-locked event-related desynchronization exclusively during externally-cued movements (Fig. 3A). The maximal desynchronization was observed 200 ms after tap onset. As beta-desynchronization was strongest between tap onset and 0.6 s after movement initiation, we calculated the average beta-power in this period for all patients. In the linear mixed effects model with subject as random effect, behavior affected the event-related beta-power ($\chi^2(1) = 9.25$, $p = 0.00235$), thus showing a significant desynchronization during externally-cued as compared to self-paced movements (Fig. 3B).

Event-related phase-synchronicity analysis

We investigated cortico-subthalamic coupling within two distinct cortico-subthalamic loops (sensorimotor: L_{SM}, associative: L_A, Fig. 4A) by calculating the phase locking value in each loop and for both motor behaviors separately. Qualitatively, we found higher synchronicity after tap onset in the sensorimotor loop during self-paced behavior. Conversely, during externally-cued movement, phase locking was higher in the associative loop. In analogy to our event-related beta-power analysis, we summarized the time-dependent signal in the period between 0 and 0.6 s after tap onset for each patient and calculated a relative measure (difference L_{SM}-L_A) for direct comparison of both presumed networks. During the externally-cued paradigm, average phase synchronicity was

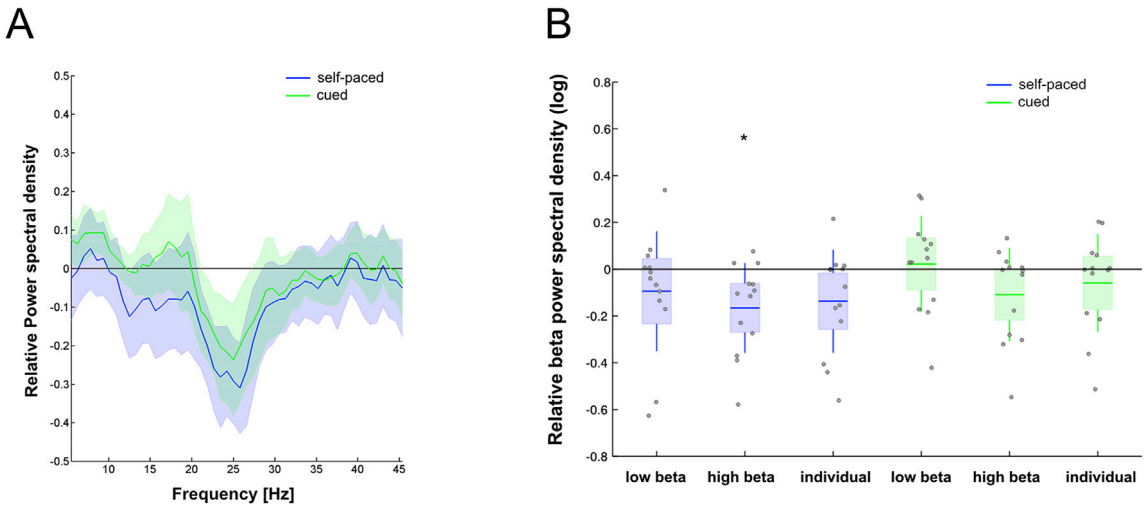

Fig. 2. a) Movement, regardless of self-paced or externally-cued tapping and with respect to rest, resulted in a desynchronization in the high beta-band (20–35 Hz). For STNs contralateral to the tapping index finger ($n = 13$), the local field potential (LFP) was recorded during 90 s periods of rest, self-paced tapping, and externally-cued tapping. Subsequently, the power spectral densities (PSDs) during the self-paced and externally-cued tapping experiments were calculated using Welch's periodogram and later normalized by the PSD during the respective period of rest. The mean and its 95% confidence interval over all STNs were plotted for the self-paced (blue) and the externally-cued (green) experiments.
b) Significant desynchronization in the high beta-band and the STN-specific band during self-paced tapping with respect to rest. Each rest-normalized self-paced and externally-cued PSD ($n = 13$ each) was averaged over the low beta-band (13–20 Hz), the high beta-band (20–35 Hz), and the STN-specific beta-band before the mean (horizontal colored line), its 95% confidence interval (patch), and its standard deviation (vertical line) for each band and for both the self-paced (blue) and the externally-cued paradigm (green) were calculated. We performed likelihood ratio tests of linear mixed effects models (subject as random effect) to determine whether behavior (self-paced tapping or externally-cued tapping) compared with the rest condition affected the averaged power spectral densities within the given beta subbands as a fixed effect (*: $p \leq 0.05$).

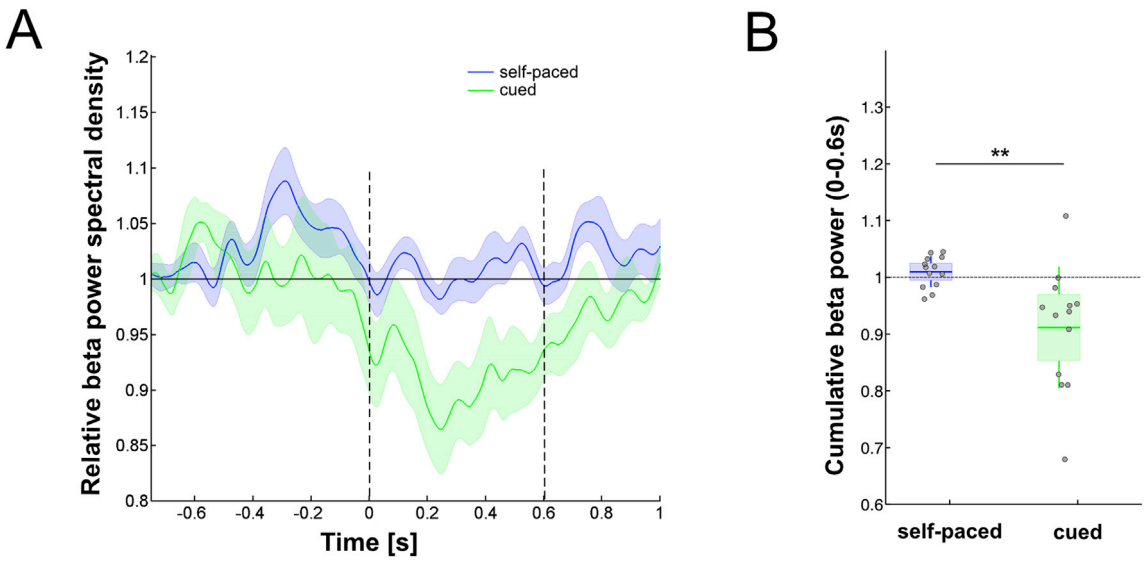

Fig. 3. a) Desynchronization in the event-related power time-course occurred exclusively during externally-cued but not during self-paced tapping. Firstly, time-frequency representations around the onset of each included tap ($t = 0$ s) and for the STN-specific band (beta-peak frequency $\pm$ 5 Hz) were calculated using Stockwell transforms. Secondly, all time-frequency representations of an experiment were voice-normalized at each resolved frequency by their mean between −1 and −0.5 s prior to point-by-point averaging. The resulting time-frequency representations were averaged across the frequency domain and the mean and SEM of all STNs ($n = 13$) plotted for both externally-cued (blue) and self-paced (green) experiments.
b) The event-related power modulation was significantly decreased after tap onset during externally-cued tapping compared with self-paced tapping. We averaged the relative power in the STN-specific band between 0 and 0.6 s for each STN ($n = 13$) (gray dots) and plotted the mean and SEM across all externally-cued (blue) and self-paced (green) experiments. Likelihood ratio tests of linear mixed effects models (subject as random effect) revealed behavior (self-paced tapping vs. externally-cued tapping) to be a significant fixed effect (** : $p \leq 0.005$), desynchronizing the event-related beta-power during externally-cued tapping experiments as compared to their respective self-paced tapping experiments.

found to be higher in the associative (L_A) than in the sensorimotor loop (L_{SM}), as evidenced by the linear mixed effects analysis (subject as random effect), where the fixed effect of loop affected the PLV ($\chi^2(1) = 6.00$, $p = 0.01433$), increasing it when comparing the associative (L_A) with the sensorimotor loop (L_{SM}) (Fig. 4C). In a systematic analysis, we calculated phase locking for all different combinations of DBS electrode locations (low/high) and EEG electrode position (frontal/central). During self-paced movement, phase locking was found to be maximal between upper DBS contacts and central electrodes. Conversely, during externally-cued motor execution we found the highest synchronicity between lower DBS contacts and frontal EEG. This inverse pattern of loop predominance for each behavior was confirmed by a linear mixed effects model with subject as random effect, where behavior (self-paced vs. externally-cued tapping) affected loop predominance (evaluated as the phase locking in L_A minus the phase locking in L_{SM}) ($\chi^2(1) = 11.07$, $p = 0.00088$). Furthermore, we found a stronger peri-movement coupling in the associative loop during externally-cued movements compared with self-paced movements, as evidenced by the linear mixed effects model (subject as random effect, behavior as significant fixed effect) ($\chi^2(1) = 7.49$, $p = 0.00619$) (Fig. 4D). Electrode positions were reconstructed according to intraoperative electrophysiological recordings relative to the upper STN border. For all included patients, the lower and upper contact pairs were located in proximity to the upper and lower STN border (Fig. 4B).

Discussion

Inspired by the clinical observation that habitual motor behavior is more severely affected than goal-directed behavior in PD patients, we investigated local field potentials in the STN and neuronal synchronicity within different cortico-subthalamic networks in PD patients performing self-paced and externally-cued finger movements. We found that only externally-cued movements induced a pro-kinetic event-related beta-desynchronization, whereas beta-oscillations were continuously suppressed during self-paced motor control. Another key finding of this study was that beta phase-synchronicity analysis revealed inverse patterns of activation in two neuroanatomical networks proposed for controlling habitual and goal-directed movements, respectively. In conclusion, this study provides electrophysiological evidence of different behavioral cortico-basal ganglia networks confirming the notion of distinctive motor control loops.

Motor paradigms

We propose to embed the examined behavioral paradigms (externally-cued versus self-paced movements) within the general theoretical framework of goal-directed and habitual motor control. Several factors are taken into consideration when determining whether a certain behavior is goal-directed or habitual: Novel tasks are initially performed in a goal-directed manner, whereas after a sufficient training phase habitual control dominates. Similarly, predictable ‘routine’ tasks are considered habitual, whereas behavior depending on non-routine decision-making are performed in a goal-directed manner (Redgrave et al., 2010). Furthermore, in animal models, reinforcement learning paradigms are usually applied to favor goal-directed or habitual behavior, respectively (Tanaka et al., 2008; Balleine and O'Doherty, 2010; Gremel and Costa, 2013). The distinction of self-paced and externally-cued movements is however subtler. On the one hand, one might argue that external cues provide stronger sensory input and therefore cued motor control is predominantly under (habitual) stimulus control. However, self-paced behavior may depend on sensory input as well (e.g. sensory feedback during walking) and recent theoretical approaches propose to define habits as predefined over-learned actions sequences (Botvinick et al., 2009; Dezfouli and Balleine, 2012). In a similar vein, using general concepts of instrumental control, habitual behavior is represented by fast, efficient, and memory-dependent internal models, whereas goal-directed behavior is controlled by explicit model-based representations of motor outputs (Daw et al., 2011; Gillan et al., 2015; Dolan and

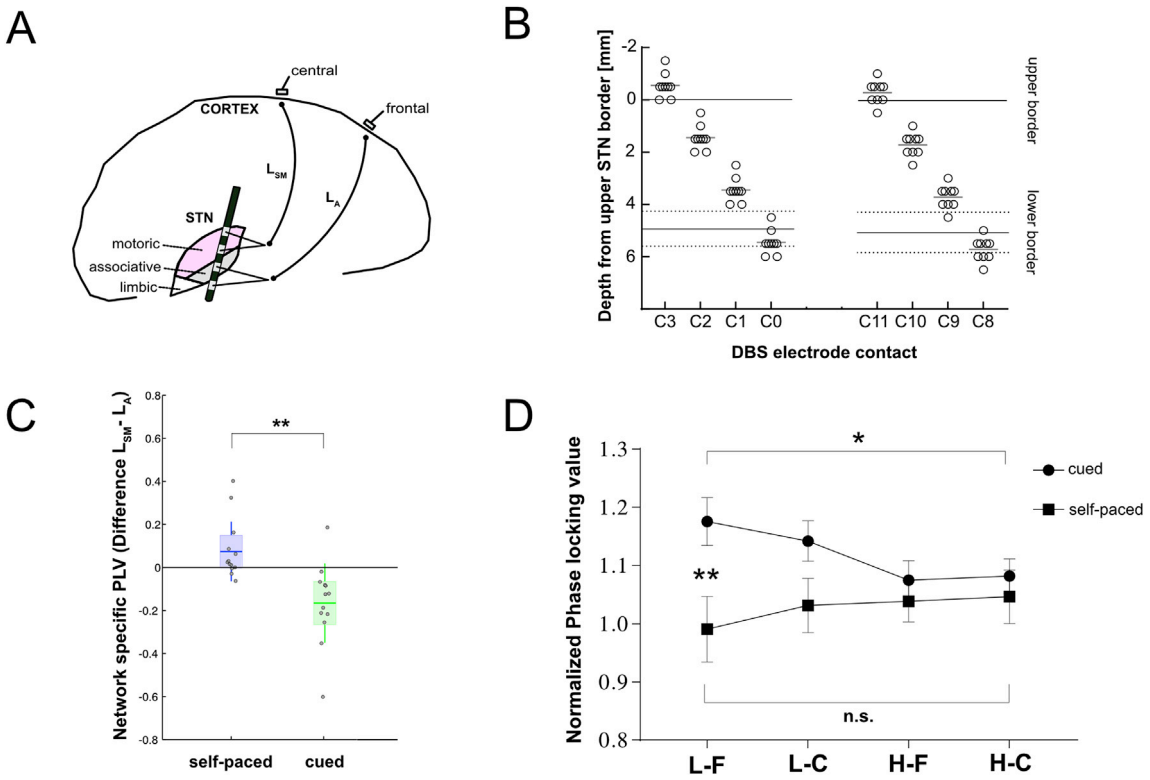

Fig. 4. a.) Schematic representation of the sensorimotor cortico-subthalamic loop, L_{SM} (central EEG–upper STN bipolar lead contacts), and the associative cortico-subthalamic loop, L_A (frontal EEG–lowermost STN bipolar lead contacts). We compared synchronicity between the two distinct loops using the phase locking value (PLV) during contralateral self-paced or externally-cued tapping.
b.) Intraoperative micro-electrode recording based lead-location reconstruction. Circles ($n = 9$ patients) represent the positions of the DBS electrode contact positions relative to the electrophysiologically determined upper STN border. Solid lines: upper and lower borders of the STN, dashed line: 95 % confidence interval of the lower border of the STN, relative to the upper border.
c.) L_{SM} network-specific PLV is increased during self-paced tapping, whereas, contrarily, L_A network-specific PLV is increased during externally-cued tapping. The PLVs were normalized to the pre-tap mean between -1 and -0.5 s and averaged between 0 and 0.6 s. Likelihood ratio tests (linear mixed effects model, subject as random effect) revealed an inverse pattern of predominant network activation (evaluated as the dependent variable PLV within L_{SM} minus PLV within L_A) with behavior (self-paced tapping vs. externally-cued tapping) as a significant fixed effect (** : $p \leq 0.001$). Horizontal colored lines: average; patched colored area: average $\pm$ 1 SEM; vertical lines: average $\pm$ 1 SD.
d.) Inverse synchronization patterns during self-paced and externally-cued tapping. L-F represents the phase-locking between the lowest bipolar subthalamic electrode derivation and the frontal electrode site (cf. L_A), H-C represents the phase-locking between the highest subthalamic electrode derivation to the central electrode site (cf. L_{SM}), and L-C and H-F the remaining STN-EEG connections. PLVs were normalized to the pre-tap mean between -1 and -0.5 s and averaged between 0 and 0.6 s. During self-paced tapping, the normalized PLV is higher in H-C than L-F, whereas during externally-cued tapping the normalized PLV is higher in L-F than H-C. Likelihood ratio tests (linear mixed effects models, subject as random effect) revealed a significant fixed effect of loop (PLV within the L_{SM} vs. L_A) during externally-cued tapping and a higher synchronization in L-F, representing the L_A loop, during externally-cued tapping than during self-paced tapping (significant fixed effect of behavior). Whiskers represent the SEM ($n = 13$), *: $p \leq 0.05$, **: $p \leq 0.01$.

Dayan). We adapted these generalized concepts to compare self-paced versus externally-cued finger tapping. We consider the externally-cued motor task to be predominantly goal-directed, because motor control in a selective GO/NOGO task relies on permanent attentive and cognitively triggered *explicit* (model-based) motor control. Self-paced movements, on the other hand, rely on internal cognitively less demanding *implicit* models representing habitual motor control. Thus, we consider self-paced finger tapping as a habitual action *sequence*, whereas repetitive auditive cues provide ongoing triggers for individual goal-directed actions.

Beta-oscillatory patterns in the Parkinsonian STN during habitual vs. goal-directed behavior

In agreement with many previous studies in PD patients, ongoing movement desynchronizes subthalamic beta-activity as compared to the resting state in both motor paradigms, supporting the outstanding role of beta-oscillations as a movement inhibitory basal ganglia signal (Fig. 2). The observed tonic desynchronization was most prominent in the high beta-band and more pronounced for the self-paced (habitual) behavior than for the cued (goal-directed) behavior. This finding can be well integrated into the proposed model of segregated networks controlling the investigated movement paradigms. Considering the movement-inhibitory effect of pathologically elevated beta-power and the behavioral observation that habitual motor control is more severely affected than goal-directed motor control in PD, we speculate that baseline (inhibiting) beta-power in the network controlling habitual behavior might be higher than in the network controlling for goal-directed movements. Ongoing habitual motor output would therefore require a stronger beta-desynchronization, as compared to only moderate beta-elevation in a less affected network controlling goal-directed behavior. The more inhibited a network is in its (pathological) resting state, the more tonic desynchronization it requires to produce motor output, as we observed in this study during the habitual paradigm.

Tonic vs. phasic beta-desynchronization

We exclusively found event-related beta-desynchronization during externally-cued movements, but only little temporal modulation during

the self-paced task (Fig. 3). Put differently, for the same motor output, we observed tonic beta-desynchronization in habitual, but phasic desynchronizations in goal-directed behavior. The observation of different patterns of beta-modulation (time-locked desynchronizations during goal-directed movement vs. tonic desynchronization during habitual behavior) provides electrophysiological evidence for distinct neuronal networks being recruited based on the movement task's nature. The neuronal signaling in the presumed networks apparently do not share the same pattern for movement activation. Interestingly, during goal-directed movement control, pathological beta-activity is repeatedly suppressed for every single movement (reflected by reduced event-related beta-powers). This phasic modulation of beta-oscillations by repetitive cues might be beneficial for movement control in PD: Whereas the poorly-modulated (continuous) beta-desynchronization in habitual motor control requires a higher amount of beta-reduction for the same effect, the 'on demand' beta-modulation in goal-directed control might be more efficient, requiring beta-desynchronizations only intermittently (at movement onsets).

Network dichotomy

To further test the hypothesis of segregated networks, we defined a sensorimotor (L_{SM}) and an associative cortico-subthalamic loop (L_A) between the presumed subthalamic subdivisions and their distinct cortical reference points and calculated phase synchronicity during the externally-cued and the self-paced motor paradigm. Due to the hypothetical origin of these networks, the exact definition of the reference points within each network is difficult. Furthermore, the spatial resolution within the STN is limited to only 4 lead contacts and the predefined trajectory of the implanted DBS lead. Nevertheless, intraoperative microelectrode recordings provided the anatomical borders of the STN along the implantation trajectory. Hence, the upper contact pair of the lead should record a more dorsolateral and the lower contact pair a more ventral and medial subthalamic signal (translating to sensorimotor and associative loops, as proposed elsewhere (Redgrave et al., 2010)). Beta phase-synchronicity analysis revealed inverse patterns of activation in the two neuroanatomical networks proposed for controlling habitual and goal-directed movements, with a higher network synchronicity in the respective network of each behavioral paradigm. In this line, a change in movement paradigm leads to a change in network activity, which might result in the different oscillatory patterns seen on the subthalamic level. These findings can be interpreted as further evidence for the activation of distinct cortico-subthalamic loops in habitual vs. goal-directed behavior, thus corroborating the current anatomical hypothesis for segregated neuronal networks concerned with either behavior. Furthermore, the predominant network activity during habitual tapping does not reach the same level of synchronicity as the predominant loop during goal-directed tapping, which might be an electrophysiological sign reflective of the selective neuronal degradation in the neuroanatomical network associated with habitual movement. Integrating these findings with the oscillatory patterns discussed above, it seems possible that short intermittent, task-related beta-desynchronizations are repeatedly cortically-driven through the associative loop whereas such cortically-driven, intermittent beta-desynchronizations are less pronounced in the habitual behavior, given its lower cortico-subthalamic connectivity and tonic beta-desynchronization.

Low- or high-beta-band activity – which beta sub-band is 'more pathological'?

As for the different beta sub-bands, it has been proposed that low-beta-activity might be more closely related to the Parkinsonian state, whereas high-beta-activity might be more closely related to physiological motor control (Wolters and Baumann, 2014). The observed pronounced desynchronization in the higher-beta-band might therefore be interpreted as a correlate for movement control in general (not limited to the Parkinsonian state), supporting the idea that segregated pathways exist in healthy and pathological brains. On the other hand, our data also showed that peak beta-activity has a strong inter-individual variability and therefore 'low'-beta in one patient could translate to 'high'-beta in another patient if strict beta-band limits are applied. This interpretation is supported by our finding that individual beta-bands revealed the highest desynchronization differences.

Implications for Parkinson's disease

We found that distinct neuronal networks are recruited during externally-cued and self-paced behavior in PD. We propose that due to relatively preserved associative cortico-subthalamic connectivity, which is activated during goal-directed movement, the increased baseline beta-oscillatory activity in PD can be overcome by intermittent, but pronounced peri-movement beta-desynchronizations. In contrast, the predominant cortico-subthalamic loop in habitual behavior requires strong and tonic beta-desynchronization, given the lesser cortico-subthalamic connectivity for oscillatory modulation. Switching from habitual to goal-directed motor control might therefore provide a twofold benefit for PD patients. First, the goal-directed network might be less affected in terms of pathological beta-oscillations and therefore less beta-desynchronization is required for the same motor output. Second, the signaling architecture in the goal-directed network allows for a more efficient (time-locked) way of beta-desynchronization, hereby allowing for better motor performance at less 'cost'. In habitual behavior, on the other hand, it is presumably more difficult to initiate and subsequently continue movement, which requires beta-oscillations in the STN to be continuously desynchronized, as only short interruptions, or strong beta-bursts, are sufficient to abruptly terminate an ongoing habitual movement.

As an important limitation, this invasive study could not be performed in a controlled manner, and the link between our findings and the pathophysiology of Parkinson's disease therefore remains speculative. It might be well possible that the observed network dichotomy in terms of modulated electrophysiological activity is indeed also represented in healthy subjects. However, even if the modulation of beta activity within different networks were a general central mechanism of motor control, a disease-specific impact on these networks could still explain changes in the network equilibrium. For example, excessive (baseline) beta-activity in Parkinson's disease could favor repetitive short beta desynchronization (as in cued movements) over longer lasting tonic beta desynchronization (self-paced).

From reinforcement learning towards motor control

In classical animal models, goal-directed and habitual behavior are typically contextualized in terms of reward-related action-outcome contingency (Balleine and Ostlund, 2007; Balleine and O'Doherty, 2010). Habitual behavior is defined as over-learned motor behavior that persists after dissociation of outcome and action (e.g. by devaluation) (D. Adams and Dickinson, 1981; M. Colwill and A. Rescorla, 1985; Gremel and Costa, 2013). This approach has proven to be very useful and valid in animal models, because a rigid dichotomy is established free from cognitive subjective measures. This procedural definition links habitual and goal-directed behavior intrinsically to reward-learning (Balleine et al., 2007). Strictly speaking, habitual motor performance can only be observed in an over-trained and later devalued state and conversely goal-directed behavior occurs only early in the learning phase. However, habitual over-trained motor behavior in humans (e.g. walking or car-driving) does not necessarily rely on cue-related and later devalued action-outcome contingency. Following human-based concepts, we therefore tried to challenge these traditional definitions and translated the concepts of reward learning into more general terms of motor control (free from learning strategies) (Redgrave et al., 2010).

Methodological aspects

The motor paradigms used for this study were not reinforced by cue-reward association. This design was chosen for several reasons. First, due to the limited postoperative time period, we aimed at providing a simple and well comparable motor task for both conditions that can be performed without prior training. Furthermore, a presented reward could interfere directly with activity in the dopaminergic system (only during goal-directed tasks) and therefore bias the measured neuronal activity directly. Because of the chosen design, we have no ultimate behavioral proof for motor habituation (i.e. presence of motor output in the absence of a previously present reward). Nevertheless, in terms of training and predictability, we argue that self-initiated finger tapping is highly over-trained and therefore more habitual, whereas motor output triggered by non-rhythmic cues represent a novel task and represents goal-directed motor behavior. As a further limitation, the experimental design did not allow for randomization of tasks, because the habitual behavior must precede the goal-directed paradigm in all patients. Thus, we cannot rule out possible confounding effects caused by attention, fatigue, or practice. Finally, we investigated time-locked and steady-state modulations of beta activity, while recent studies also showed spontaneous temporal fluctuations of beta activity (beta-bursts) (Tinkhauser et al., 2017). Therefore, the duration and variability of beta-bursts might have indirectly influenced the observed beta-modulation during the motor tasks.

Conclusion

This invasive electrophysiological human study provides evidence for the existence and recruitment of distinct neuronal networks during habitual and goal-directed behavior in PD patients. We interpret our findings as a direct correlate of the proposed dichotomous neuroanatomical networks controlling habitual and goal-directed behavior.

Author contributions

Conceptualization: O.B., R.G., D.W., C.R.B., and L.L.I; Methodology: O.B., R.G., C.R.B., and L.L.I; Software: O.B. and L.L.I; Formal Analysis: O.B. and L.L.I; Investigation: O.B., L.S., M.U., H.B.V., and L.L.I; Resources: R.G. and C.R.B; Writing – Original Draft: O.B. and L.L.I; Writing – Review & Editing: R.G., L.S., M.U., H.B.V, and C.R.B.; Visualization: O.B. and L.L.I.; Supervision: R.G., L.L.I., and C.R.B.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.05.012.

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